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DISPOSABLE DIALYSIS DEVICES: IS REUSE ABUSE?

HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

NINETY-NINTH CONGRESS

SECOND SESSION

WASHINGTON, DC

MARCH 6, 1986

Serial No. 99-15

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DISPOSABLE DIALYSIS DEVICES: IS REUSE ABUSE?

THURSDAY, MARCH 6, 1986

U.S. Senate,
Special Committee on Aging,
Washington, DC.

The committee convened, pursuant to notice, at 10 a.m., in room SD-628, Dirksen Senate Office Building, Hon. John Heinz (chairman of the committee) presiding.

Members present: Senators Heinz, Chiles, Johnston, Pressler, Grassley, and Hawkins.

Staff present: Stephen R. McConnell, staff director; Robin Kropf, chief clerk; James Michie, chief investigator; David Cunningham, investigator; David Schulke, investigator; Isabelle Claxton, communications director; Sara White, communications assistant; Diane Lifsey, minority staff director; Chris Jennings, legislative assistant; Kimberly Kasberg, hearing clerk; Diane Linskey, staff assistant; and Dan Tuite, printing assistant.

OPENING STATEMENT OF SENATOR JOHN HEINZ, CHAIRMAN

Chairman Heinz. Ladies and gentlemen, good morning. This hearing of the Special Committee on Aging will come to order.

Our committee, the Senate Special Committee on Aging, has just completed a 4-month investigation into the reuse of disposable dialysis devices. Copies of the full committee staff report [1] are available here today.

For the 78,000 Americans with end-stage renal disease, this plastic filter and these plastic tubes symbolize a $13 circle of life. Three times a week, 52 weeks a year, dialysis patients hook up with these devices to kidney machines for life-saving dialysis treatment.

In each 4-hour session, blood flows through this filter, the dialyzer traps the toxins, salt, and water and pure blood is returned to the patient.

Congress established Medicare funding for dialysis patients of all ages in 1972. I was privileged to be a member of the conference between the House and Senate that wrote that legislation.

Today, Federal spending runs over $1.5 billion on this program. Clinics are reimbursed under Medicare on the basis of one-time use—and I emphasize one-time use—for single use, only, as it says right on the labels, of these disposable filters, blood lines, and other devices. The manufacturer labels those items very clearly, as we've just seen.

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[1] See appendix, p. 99.

An investigation by this committee indicates that more than 60 percent of dialysis clinics reuse filters up to 30 times, flushing out and disinfecting them with a chemical solution. Reuse creates a financial windfall for many clinics.

An Office of Technology Assessment study indicates clinics pocket $80 million per year in excess profits through reuse of filters alone. So you could say that simple greed gives birth to a standard practice, and one of modern medicine's greatest achievements of life emerges as a machine, as we will hear, for suffering and even death.

The truth about reuse is that it does expose tens of thousands of dialysis patients to dangerous and unnecessary risks. Over 85 percent of reuse clinics disinfect dialysis devices with formaldehyde, a potent toxin. It's known to cause cancer, liver damage, and destruction of red blood cells.

Residue of formaldehyde left behind in a so-called sterilized dialyzer can leach out into the patient's blood stream, silently contaminating even clean blood. Exposure to deadly bacteria—plastic particles eroded from the tubing—and reduced efficiency with repeated sterilization are other risks inherent in reuse.

Given these risks, it is unconscionable to me that some dialysis clinics actually blackmail patients into reuse, threatening to end treatment if they refuse to submit. Well, with that kind of ghoulish greed, clinics pocket the profits and let the patient be damned; and that's not right.

Almost 8 years ago Congress mandated a study by the National Institutes of Health of reuse of dialyzers to determine safety. The National Institutes of Health has yet to deliver a final study to the Congress, 8 years later.

The Food and Drug Administration and the Health Care Financing Administration, as well, have thoroughly abdicated their responsibilities to insure safety, efficacy, and quality in care in dialysis. For almost 25 years, we've been operating a national program without clinically validated guidelines; and, lacking clear guidelines, we risk the lives of individuals already living in fear for life.

There seem to be no explanation for this dilemma beyond the blatant unwillingness of the Federal agencies involved to say something as simple as "The buck stops there."

In the midst of this turmoil and uncertainty, the Health Care Financing Administration is considering reducing reimbursement rates by roughly $10 per dialysis treatment. This proposed reduction would work out to about 80 percent of cost of this $13 kit that is reimbursed for each dialysis treatment by the Medicare through the Health Care Finance Administration. Such a reduction, based predominantly upon audits of centers which practice reuse, tightens the vice on patients caught between the need for informed choice and Federal policy driving profits.

This committee was pleased to learn that the Food and Drug Administration is considering, at some considerable delay, applying the good manufacturing practice regulations to those who reprocess disposable dialysis devices. That's an important beginning, but it's not an end to the FDA's fulfilling its obligation to these very vulnerable dialysis patients.

We have a full morning of witnesses. I'm very pleased to see that my friend and colleague, Senator Bennett Johnston of Louisiana, is here to welcome a constituent, who is one of our witnesses. First, Senator Johnston will deliver his opening remarks.

Then what I would propose to do, Senator Johnston, is call the witnesses to the table and afford you the opportunity to introduce someone that is here from Baton Rouge.

STATEMENT BY SENATOR J. BENNETT JOHNSTON

Senator JOHNSTON. Yes. Thank you very much, Mr. Chairman. I do have a short opening statement.

Mr. Chairman, I am pleased that the Special Committee on Aging has scheduled this hearing to explore whether the reuse of disposable dialysis devices is dangerous under existing clinical practices; and whether uniform Federal standards should be developed to control both the reprocessing and reuse of these devices.

I would also like to take a moment to welcome my constituent, Malcolm Shuman of Baton Rouge. Mr. Shuman's mother passed away as a result of an infection she acquired while undergoing dialysis treatment in a Louisiana clinic.

I look forward to hearing his testimony and hope that the committee's interest in this matter will encourage Federal officials to issue regulations which will deter such accidents from occurring in the future.

Today, more than 78,000 individuals who suffer kidney failure receive dialysis treatment in over 1,200 clinics across the Nation. More than one-half of these clinics reuse dialyzers and many times this equipment is reused 20 to 30 times despite the fact that it is clearly marked, as you pointed out, "For single use only."

These clinics sterilize the equipment after each use with a solution of formaldehyde and water. Tests have shown that formaldehyde causes cancer and liver damage, and oftentimes formaldehyde residue remains in the dialysis equipment and is subsequently leached into the patient's bloodstream.

It may very well be that our Medicare reimbursement schedule encourages the practice of reuse. Under current law, a dialysis clinic is reimbursed the same rate regardless of whether it reuses the disposable equipment. As you point out, Mr. Chairman, every reuse saves the clinic approximately $10 for a new dialyzer and $3 for new blood lines.

Unfortunately, it appears that the Federal Government has simply dropped the ball on this issue. Over the years, a number of agencies, including the FDA and the HCFA, have begun to study whether it is safe and efficacious to reuse dialysis equipment. However, none of these studies has been completed and neither regulations nor guidelines for reuse have yet been promulgated.

Mr. Chairman, I fear that these practices are exposing many dialysis patients to unnecessary risk. At the same time, with proper regulation, reuse may constitute a medically acceptable and cost-efficient procedure.

Hence, at the very least I hope that this hearing will impress upon the agencies the need to revisit this issue. I look forward to reviewing today's testimony and working with the committee in exploring this issue in further detail.

Thank you, Mr. Chairman.

Chairman Heinz. Senator Johnston, thank you very much. We are delighted to have your constituent, Dr. Shuman, here from Baton Rouge.

Senator Glenn could not be with us, but he has asked that his opening remarks be made a part of our record.

[The prepared statement of Senator Glenn follows:]

Statement of Senator John Glenn

I am pleased that the Senate Special Committee on Aging is holding today's hearing on the reuse of hemodialysis devices in the treatment of Medicare beneficiaries suffering from End Stage Renal Disease.

Over 60 percent of the more than 1,200 dialysis clinics in this country reuse dialysis devices. However, there are no uniform medical or federal standards regarding how these clinics should sterilize dialysis equipment for reuse. Consequently, different mixes, strengths of solution and types of protocol are used for sterilizing dialysis devices, and this raises quality of control concerns.

After months of study, the Aging Committee has uncovered some disturbing findings which question the federal government's commitment to ensuring that the care of thousands of dialysis patients is not being compromised by the practice of reusing dialysis devices. Two central questions that consistently and logically emerge are:

(1) Why have the Food and Drug Administration (FDA) and the Health Care Financing Administration (HCFA) neglected to carry out a proper clinical study on a widespread practice that impacts thousands of dialysis patients?

(2) Why aren't there uniform federal standards which govern the reuse of these devices?

Before turning to today's witnesses in an attempt to answer these questions, it is important to place this hearing in its proper perspective. Clinics across the country have been reusing dialysis devices for years. With the exception of a number of deaths at one Louisiana clinic that may be associated with improper sterilization practices, we are not aware of other similar problems. In fact, medically speaking, some patients respond more positively to reused devices than to new products. The great number of patients who receive dialysis in clinics that reuse devices should be assured that we are not holding this hearing to condemn reuse. We simply would like to know why the FDA and HCFA have taken the position that funding a clinical study is unnecessary. From what we now know, it appears obvious that such a study would answer many of the questions which will be raised today.

This is not a new issue. Congress has been concerned about possible problems associated with the reuse of dialysis devices since the late 1970s. The Social Security Amendments of 1978 mandated that the Secretary of Health and Human Services study the medical appropriateness and safety of cleaning and reusing dialysis filters. Congress still has not received a complete report which includes clinical trials of resterilized dialyzers.

Dialysis is a life-saving medical technique which has been practiced for over two decades. This procedure now serves 78,000 patients and costs the Medicare program in excess of $2 billion a year. At a time when we are spending so much money to help this many people, doesn't it make sense to ensure that the services provided to these patients are safe and effective?

I look forward to today's testimony, and thank the witnesses for their participation and assistance.

Chairman Heinz. Let me ask if the witnesses—Melinda McFadden from Philadelphia, Robert Rosen from Bensalem, Dr. Shuman, and Mr. Vagn Vogter—would please come forward and take their places at the witness table.

I would like to welcome, especially, two of my constituents: Melinda McFadden from Philadelphia and Robert Rosen from Bensalem. We are privileged to have both of you from the Philadelphia area.

Mr. Vagn Vogter, you have come almost as far as Dr. Shuman. You have come from St. Petersburg, and we welcome you as well.

I think what I would like to do is ask Ms. McFadden to please proceed with your testimony, and then we will go through the panel in turn.

STATEMENT OF MELINDA McFADDEN, PHILADELPHIA, PA

Ms. McFadden. Good morning, everyone. My name is Melinda McFadden. I have been a dialysis patient for 8 years.

Five years ago, my unit decided to go to reuse without any warning. We were not told of alternative means of dialysis. We were told that every unit across the country and the hospitals would be reusing.

I made the decision to stay at that unit because I had been there 3 years. I had a brother who was there for 10 years.

When I began to question the reuse, how it made me feel, I was told if I did not like it there I had to go someplace else. I was told, on numerous occasions, that formaldehyde did not get into the bloodstream; that the Federal Government did not pay for dialysis payments, but the State government did; so, therefore, they had to reuse in order for us to come there.

I was told that if I did not agree to reuse I would have to leave right then and there. When I was asked to sign the paper for permission to reuse, I asked the head nurse, could I take the paper and read it over with my doctor. I was not allowed, no, I could not. If I did not sign then, I had to leave the unit right then.

I needed my treatment so I went on and signed, and got on the machine. In November I was given an increased dose of heparin because I have a bleeding problem and I went from 2,000 milligrams to 6,500 milligrams in the first hour and 1,000 in the second hour, which caused my side to bleed up to 1 hour when I got off the machine.

I asked a doctor, I said, why save the dialyzer? Why not save me? He told me if I did not like reuse, I had to leave the unit and look for someplace else to go. I asked him where could I go? He told me he did not know, but I could not stay there if I did not want to reuse.

I have seen many problems with reuse. I have been very sick with reuse. When I first started on dialysis, I used to work and go to school. I had to give up my job. Now I just attend school and it is really too much for me, but I go anyhow.

I don't have the energy that I used to have. When I get off the dialysis I have to call home and have someone meet me at the door to help me up the steps into the bed because I cannot stand up.

I have severe headaches every Monday, Wednesday, and Friday. I take strong medication right after dialysis. I have to take a pill as soon as I get off because I have such a bad headache from the reuse.

We were not told of side effects until later. As I said, I have been on dialysis 8 years; 5 years we have been reusing. We have never been given a piece of paper that says reuse causes these side effects.

What we were told was that all clinics and the hospitals were going to reuse, and we could go someplace else if we did not want to stay there.

I am not the only patient who suffers from reuse. I have itching problems from reuse. I faint a lot from reuse. In reusing the dialyzer, they have to turn the machine up higher in order to get more poison and more fluid off of me, and that makes me weak, sick, nauseated, and dizzy.

Chairman HEINZ. Ms. McFadden, thank you very much for your testimony.

Ms. MCFADDEN. You're welcome.

[The prepared statement of Ms. McFadden follows:]

STATEMENT OF MELINDA McFADDEN

Good Morning. My name is Melinda McFadden, I have been a dialysis patient for the last eight years. I have attended the same unit for the same period of time. Five years ago, in 1981, this unit decided to use kidney dialysis reuse, with very little warning to the patients. The only information we received was that we really had no choice, but to accept reuse. Because eventually every unit in Philadelphia would switch to reuse. We were not given a choice, nor were we informed of alternate programs to reuse. Neither were we provided with a list of centers that did not reuse.

In addition, we were not informed of possible side effects. We were not asked to sign a consent form until July, 1985. By this time I did not feel as well as I had been feeling prior to reusing. I refused to sign the form until I had spoken with my physician, since after reading the form, there were certain things I did not agree with. One of which was the statement that any doctor could examine and administer to me in a crisis. This was on a Monday, two days before my scheduled doctor's appointment. I was not given the form, but was allowed to get my treatment. On Wednesday, when I walked into the unit, I was confronted by the head nurse who took me into the hallway and informed me that the nursing director said I could not get my life-saving treatment, unless I signed the form right then. I could not discuss it with my doctor and, if I didn't sign I had to leave the unit. I signed the form because I didn't feel well and I needed my treatment. I have been complaining about the way reuse makes me feel to the doctors, but they have informed me that this was a reuse unit and if I did not like it I could leave and go someplace else. I have not been as well as I was when I did not reuse, and I believe with all my heart that reuse is making me sicker. Thank you.

Chairman HEINZ. Mr. Rosen.

STATEMENT OF ROBERT ROSEN, BENSALEM, PA

Mr. ROSEN. My name is Robert D. Rosen. I am chairman of the National Kidney Patients Association in Feasterville, PA.

I would like to open my remarks with a statement regarding my views on the reuse of medical disposables. I am not here to seek a ban on the reuse of these devices. I believe that if they can be reprocessed or remanufactured in a way that produces an end product which is sterile and unadulterated, then I can see no reason that it would not be acceptable.

I am a patient and I have been tied to an artificial kidney machine for over 15 years. Three times a week for the rest of my life I must receive my dialysis treatments. I am frustrated, disgusted, and upset about the Government's role in this very costly program known as ESRD.

Medical devices are being used contrary to the manufacturer's recommendations and there are no verifiable safe standards in the entire country which can guarantee the safety, sterility, and efficacy of these products once they are reused.

In light of this, patients are being forced to accept substandard, blackened, and otherwise adulterated devices as opposed to the sterile items being paid for by the Government. Patients are not given a choice.

They are being coerced, threatened, intimidated, and finally denied their life-sustaining treatment.

One of the patients in Pennsylvania who was questioned in the reuse in his unit was forced to have his treatment performed for 4 hours, three times a week while he was facing the wall. This type of complete sensory deprivation is a common practice to force patients to succumb and accept reuse.

I became interested in the reuse in medical devices in 1982 when my unit began to discuss the possibility of instituting that program. I was concerned because prior to that time my physicians had warned me that reuse was considered by them to be dangerous and it would shorten my already-impaired life span.

I started to write governmental agencies. I corresponded with all levels of the FDA, Health and Human Service, HCFA, my network, and the Department of Health in Pennsylvania. I was astounded.

The answers to my letters were an insult to my intelligence. Governmental agencies that were established in order to protect the people took great pains to mislead and confuse me.

After a short while, it became obvious that all my letters were being sent to the same person or group, and no matter what questions I asked the same word-for-word answer was being set, especially the letters received from the FDA, Health and Human Services, and HCFA.

They were demeaning and condescending.

No one can attest to the volume of formaldehyde entering a patient's bloodstream after a treatment with a reused dialyzer, yet Dr. Villarroel, in his letter of October 22, 1982, tried to assure me that trace amounts of formaldehyde do not pose a danger to patients; yet NIOSH states that formaldehyde is a dangerous carcinogen and mutagen.

Most of my letters from these agencies state that enough information for the FDA to approve reuse is not available. So until results of continuing studies are received, they will not establish a policy. That makes the patient an unwilling victim of a medical experiment, a guinea pig: nothing more.

How would you like to be told that if you do not become part of a medical experiment your physician will let you die? Furthermore, how would you feel if when you tried to appeal to the various Government agencies you were informed it was an unaccepted, but common practice, and they have no authority; but if something bad were to happen that I should sue my physician.

Corporations have completely taken over the renal field. In Pennsylvania, Washington, DC, Delaware, Florida, and most other States, there exists a medical monopoly.

Reuse is a corporate decision based upon nothing more than profits. Quality care has become a thing of the past as decisions are being made for cutting services to get a few dollars more.

I wish to remind this committee that the reuse of dialyzers has spread to the reuse of other medical disposables. It has become common practice to reuse items such as blood lines and transducer filters.

In the case of the transducer filters, no attempt is even being made to clean them after being used. They remain on the machine from patient to patient.

The purpose of that device is to protect the machine from the patient's blood entering in the case of a malfunction. It costs a mere 26 cents.

In all cases, the Government is paying the same rate for new and used. There is no saving whatsoever for anyone other than the corporation or the physician-owner who ends up cutting costs and, therefore, increasing profits. There is no provision in the system to return the savings to the Government or the third-party payer.

Under the current set up, quality providers are penalized for their use of sterile items in accordance with its labeling. Therefore, we must have Federal standards that are enforceable, verifiable if we are to permit the reuse of medical disposables.

If a product is to be reused, then it must measure up to certain standards. Good manufacturing practices, which are dictated by the FDA, are essential.

The patient must be granted informed consent without the fear of reprisals or denial of his life-sustaining treatment. I am not speaking for myself, alone, but for the 78,000 patients in the country whose very lives are in jeopardy.

Our organization corresponds and speaks to patients throughout the United States. The problems are real and they are duplicated in each and every State.

Thank you for your attention and giving me this opportunity to speak openly and freely today.

Chairman HEINZ. Mr. Rosen, thank you.

Dr. Shuman.

STATEMENT OF MALCOLM SHUMAN, BATON ROUGE, LA

Dr. SHUMAN. Good morning. My name is Malcolm Shuman.

In 1974, my mother, Elaine Menville Shuman, was diagnosed as suffering from polycystic kidney disease. She was, at that time, 61 years old, a widow and living alone. In June 1980 she began hemodialysis treatments at a local clinic.

For the next 2 years, my mother was dialyzed three times a week. While there were some periods of debility owing to the need to have fistulae surgically created in her limbs for the dialysis treatments, on the whole my mother was an active and productive person, and more often than not drove herself to the dialysis unit.

During this period, however, several things occurred to gradually turn my impression of this facility from one of trust to one of severe apprehension. From the first, there was evidence of poor supervision of technical staff. Further, the technicians frequently experienced difficulty inserting the dialysis needles into my mother's veins.

On December 4, 1981, my mother was misconnected to the dialysis machine: that is, venous and arterial tubes were reversed. On May 26, 1982, while my mother was hospitalized to have a new shunt installed, personnel from the dialysis unit forgot to come to the hospital on her scheduled day and she was not dialyzed at all.

My mother's records indicate that in late March 1982 she began the reuse of her dialyzer and the practice of reuse continued into August 1983. During the week of July 4, 1982, my mother developed a low-grade fever that persisted on and off for the next 6 months.

Investigation by the Centers for Disease Control later revealed this to be part of a widespread *Mycobacterium chelonei* infection at the facility in question. My mother was treated by antibiotics into early 1983 at which time she developed anorexia, nausea, and gastrointestinal complaints that caused her to become hospitalized.

Thereafter, with the exception of a few weeks out of the hospital with 24-hour nursing care in the summer of 1983, my mother's decline was gradual but clear. She died on September 12, 1983.

It was only in July 1983, 2 months before my mother's death, that I read an article in the local newspaper that revealed the extent of the *Mycobacterium* outbreak in the local clinic. It was then that I became acquainted with the issue of dialyzer reuse.

It was also only then that I learned, through a July 26 television news report, that the dialysis facility had apparently recently terminated one of its technicians for negligence. If that were not enough, in July 1983 the clinic's air-conditioning unit failed.

Senator Johnston, I don't have to tell you what it is like in July in Louisiana. For several weeks, anyone visiting that facility was treated to the incredible spectacle of seriously ill people lying on the floor in the waiting room in 100-degree heat while small table fans directed hot air at them.

Interestingly, the only reason given for such a long period without air-conditioning was the offhand comment of one of the nurses that the company was "* * * too cheap to have the unit fixed." Not surprisingly, this was the same company that in the spring of 1982 saw fit to send scare letters to each of its patients, including my mother, warning them that if administration proposals on the reduction of hemodialysis benefits passed, they, the patients, could be left without treatment.

After communication with my Congressman, I was enlightened to discover that what was really at risk was this company's profit structure.

It is no easy matter to care for a loved one who is in constant pain and to see that person's once-splendid mental faculties deteriorate. It is painful to see a person waste away before one's eyes.

What is more difficult, however, is knowing that this situation might have been averted or at least delayed significantly had it not been for the factors of human incompetence and greed.

I am certain that my mother was never fully apprised of the pros and cons of dialyzer reuse, but even had she been, what option did she have? When the story of the 13 deaths at this clinic first erupted in the news media and I brought the morning paper to my mother's bedside, her reaction was one of amazement followed by abject fear.

"Malcolm, for God's sake, be careful," she warned. "I'm in the power of these people."

There could be no more eloquent testimony of the duress under which she felt herself. Like the proverbial gambler, she was forced to play in the only game in town except that her weakness was a biological one over which she had no control. The same cannot be said of the clinic's administrators.

Courts of law can accord redress for injuries, but they cannot restore human life or erase the memory of pain. How very much better it would be if the disciples of greed could be removed from the practice of medicine. How much better it would be if the clients of dialysis clinics could be treated as patients and not as prisoners.

How much better if, in the future, some semblance of uniformity and vigilance could be brought to bear to protect those who have nowhere else to turn.

Thank you.

Chairman HEINZ. Dr. Shuman, thank you very much for that extraordinarily eloquent testimony.

Mr. Vagn Vogter.

STATEMENT OF VAGN VOGTER, ST. PETERSBURG, FL

Mr. VOGTER. Thank you. Prior to undergoing a kidney transplant 11 months ago, I was a dialysis patient for 27 months in an in-center dialysis unit in Florida. The machines were more than 10 years old, which caused daily breakdowns. This can be compared to an overused aircraft with no Federal standards and controls of this high-risk equipment.

The stamped "one-time-only use kidney" is used 20 times or more resulting in poor blood chemistry and overload of fluid when leaving the unit after 4 hours of treatment. I have a chart that I have made up for that, which took me about a year and a half.

In the old reused kidney, many of the fibers are blocked with old blood which can be seen as dark colors and streaks. The blood lines are reused 30 times or more resulting in poor connections and tiny holes in the lines which can let air enter slowly into the system with devastating effect on the patient.

Furthermore, tiny pockets of formaldehyde are often left in old kidneys and require a longer washing time on the machine. Not always is the formaldehyde completely removed.

I had a severe reaction from an old kidney which had been stored for a week and then reused on me. When I asked the nurse to limit the reuse of kidneys and blood lines, I was told to go somewhere else for treatment.

I offered to pay for the new kidney, but she said this was not possible.

It is important to have Federal standards to combat this careless treatment of patients, and it should be required to have the patients' informed consents for reuse.

In the center I hardly ever saw a doctor. I have my own nephrologist whom I saw once a month. I complained about the 12,000 units of heparin the nurse gave me and the doctor put me on tight heparin which resulted in fewer kidney reuses.

I have a transplanted kidney now and I am doing very well. When I first wanted a transplant, I was told I was too old—61 years old. Then I found out a 63-year-old woman had been transplanted. So I told my doctor and he finally agreed to recommend me.

I think the modules of different treatments should be explained to the patient in detail so they can make their own decisions. Thank you.

Chairman Heinz. Mr. Vagn Vogter, thank you very much.

Before we proceed to questioning, I want to recognize another very important member of this committee, a very active member of this committee, Senator Larry Pressler of South Dakota.

Senator Pressler, if you have an opening statement, please proceed.

STATEMENT BY SENATOR LARRY PRESSLER

Senator Pressler. Thank you very much, Mr. Chairman. I shall place my opening statement in the record and I ask unanimous consent to do so.

Chairman Heinz. Without objection, your entire statement will be a part of the record.

[The prepared statement of Senator Pressler follows:]

Prepared Statement of Senator Larry Pressler

We are here today to examine the risks associated with reusing disposable kidney dialysis devices. In my State of South Dakota, approximately 150 individuals are currently dialyzing in facilities or at home. That may not be a great number of people, but it is of grave importance to those 150 and their families. We have six Medicare certified dialysis units, of which only one is practicing reuse. In this facility, a device is reused, on average, eight or nine times. However, in South Dakota and around the Nation, reuse is increasing. Therefore, it is essential that we look at the possible effects of this increasingly popular, yet potentially dangerous practice.

In looking over the testimony, I would have to agree with Dr. Wolf's endorsement of the "uncertainty principle." That is, if we are not sure whether reuse is right or wrong, we should not be practicing it. This certainly applies in this case, where human lives could be at stake.

As I understand it, units are reimbursed as if they were purchasing a new device each time. Also, these devices clearly state "for single use only." I must believe that manufacturers have a better reason than outright greed for issuing this warning. Given the fact that the devices being reused cost about $13, it does not seem unreasonable to provide patients with new dialyzers for each treatment—especially given the reimbursement rates: $131 for hospital based clinics, and $127 for nonhospital based clinics.

In closing, a controlled clinical study by the Department of Health and Human Services on the effects of reuse should be undertaken immediately. The FDA should adopt uniform minimum standards for reprocessing and reuse of disposal dialysis devices. And, most importantly, patients should not be forced to reuse.

Senator Pressler. Let me commend Senator Heinz for his leadership on this issue and commend the staff for this fine report, which I have just read. The recommendations of the staff should be addressed in the form of questions to the witnesses here today. If the Department of Health and Human Services cannot establish a uniform Federal standard for the reprocessing and reuse of the disposable dialysis devices, then I believe we should require that they not be reused. It is an abuse that we need to correct if we find that it is true.

Let me also say that in my State of South Dakota we have six Medicare-certified kidney dialysis units, of which only one engages in reuse. I am not in any way criticizing that one, because it may use procedures that are acceptable.

But I am reminded of years ago when I was in the Army in Vietnam. To economize, certain medical services to soldiers were eliminated. At a time when we were spending money hand over fist on new weapons, $15 a soldier was saved by not giving a gamma globulin shot to certain troops.

The reason for it was that it was cost-saving; we do save money in very funny places. This situation is analogous: saving $13 on sick people—and money is lost elsewhere.

So I do want to commend our witnesses. I am going to ask them some questions based on the staff recommendations.

Again, I want to commend the staff who worked on this report; I think it is excellent.

Chairman HEINZ. Senator Pressler, thank you very much.

Ms. McFadden, you have testified that you did not feel well after your treatment with the reused dialyzer; that you felt very tired and drained of energy; that it has been very difficult for you to go to school and get the education and training you want; that you really feel quite sick at times after reuse; that you have experienced some difficulties so that your heparin dose has had to have been increased so much so that you even bleed at times for long periods; and all that you indicated in your opening statement.

Were you made aware of the fact—did anyone tell you that Federal guidelines provide for a grievance procedure at your clinic and at all dialysis clinics? Did your clinic tell you about this right to have your complaints addressed?

Ms. MCFADDEN. No; they did not. They don't tell us anything.

If we get any information, it is sent out in a flyer and left on the desk. Anyone can come in and pick it up.

What we were told was that everyone was going to reuse. We had no choice. We could reuse there or go someplace else.

About 3 months ago there was a flurry of activity about reuse and getting patients to sign for reuse. I had never signed, but yet I was on reuse. When I refused to sign, I was told that I had to leave the unit right then or sign.

I said, "Well, my doctor's appointment is this afternoon at 4. Let me take the slip there, go over the contract with them, and then I will sign it after he explains it to me." "No," the head nurse said, "you cannot do that. You sign it now or you leave off our property now."

Chairman HEINZ. Every piece of medical equipment, whether it is the dialyzer or, if you will, the artificial kidney, the filter, or this plastic tubing is clearly marked "For single-use only."

Do you ever have a chance to see these labels? Have you ever seen them around the clinic?

Ms. MCFADDEN. We see the tubes after they have been opened and taken out of the plastic. They take them out in the bag and tie them up, and then bring them to the unit and hand them to the technicians to put on the machines.

Chairman HEINZ. But they never let anybody see that label that is on every single piece of equipment.

Ms. MCFADDEN. No.

Chairman HEINZ. Mr. Vogter, in your testimony you stated that the reuse of blood tubing can have devastating effects on the patient. Can you share with us what some of those devastating effects are?

Mr. VOGTER. What happened, after 30 reuses or more the lines become hard and inflexible, and the connection that is normally a fitted connection becomes very loose and it is only held together with a piece of tape.

I have seen many times in this 27-month period that these lines bust apart in the connection because they are so rigid, and the patient loses a lot of blood.

Chairman HEINZ. Now, while you were a dialysis patient, I understand that you collected data on the lab work done on your blood chemistry. Could you tell us what you learned from that?

Mr. VOGTER. First of all, I learned that when I left the unit I was not really dialyzed clean, and it also posed a health hazard in addition to the other hazards posed by being dialyzed.

Chairman HEINZ. How did you learn that?

Mr. VOGTER. Well, when I came home I was a pound over what I should be and, also, I compared by blood chemistry before and after; and, also, when I had a brand new kidney, my blood chemistry was at the level where it is supposed to be.

After 20 uses or more, my blood chemistry was too high for a person to have, much too high.

Chairman HEINZ. Also in your written testimony, you stated that patients should be provided with informed consent for reuse of their devices. Could you tell us what you think should be in such an informed consent document?

Mr. VOGTER. The most important thing is to make the patient aware of the risks involved by reusing the lines and the kidney.

Chairman HEINZ. Dr. Shuman. By the way, Senator Johnston informs me that you are an anthropologist, not a medical doctor.

Dr. SHUMAN. Yes, sir.

Chairman HEINZ. You are a very acute observer of your fellow man. Perhaps that accounts for the clarity and articulateness of your testimony.

Could you tell us or remind us how soon after your mother began dialysis at the clinic the bacteria outbreak occurred?

Dr. SHUMAN. Well, Senator, from the medical records it would appear that the doctors' orders for reuse were first issued, in my mother's case, on March 29, 1982 and she began reuse very early in April. According to the CDC report, the first illnesses began to show up in April 1982.

Chairman HEINZ. So almost immediately after she began to reuse, people there began to get ill.

Dr. SHUMAN. Yes; other people. Her illness did not become manifest until July 1982.

Chairman HEINZ. When your mother began to reuse her dialyzers, can you recall anyone discussing this with her or, for that matter, with you?

Dr. SHUMAN. I don't recall it, Senator. I am her only child and, therefore, we discussed most important issues very thoroughly. I feel that the case was probably that the consent form was given to her with a very brief explanation such that she did not consider it significant to mention it to me because I believe, had she considered it significant, that she would have said something.

Chairman HEINZ. Mr. Rosen, in your very thoughtful and complete statement, for which I thank you, you made references to Federal agencies. You have written letters to all the Federal agencies and the Department of Health and Human Services concerning their policies on reuse.

Could you share with us, in your own words, what the policies of these agencies are?

Mr. ROSEN. The common thread that I found running through all of their answers is that we do not have any policies or guidelines on the reuse of these devices. It is just everyone is let go in their own direction to do what they want to do as far as the physicians in the units are going.

The thing that upset me more than anything was that the FDA and Health and Human Services informed me that I, as a dialysis patient, in the issue of reuse am out of the jurisdiction.

I would like to know whose jurisdiction it is in.

Chairman HEINZ. In your statement, you emphasized that reuse is a corporate decision based on nothing except greed. Could you please elaborate and tell the committee what you mean by that statement?

Mr. ROSEN. Yes. Let's say that we have unit A that they reuse and we also have unit B that they do not reuse. They are being paid exactly the same for both per treatment.

Now, for the units that they are reusing they are pocketing the difference. It is going right into their pockets. The facilities that don't reuse are doing a good job.

I have been alive on dialysis for 15 years and I have very few complications from it, and I am very active and I go all over the country about this. The facilities that do not reuse do it by the label.

What I heard you say earlier was that we may have to cut the reduction by $10. I certainly hope you mean two reimbursement rates: one for the ones that reuse and one for the ones that do not reuse. They should not be touched.

Chairman HEINZ. What I said was that it was my understanding that the Health Care Financing Administration was considering a reduction in reimbursement rates and, as I understand it, across the board.

Mr. ROSEN. But that would be unfair to that particular group of units that do not reuse, and that would punish those patients dramatically. Then you are forcing the entire country to go to a procedure that we don't have any standards for.

Chairman HEINZ. That is the reason for this hearing.

Mr. ROSEN. I would like to see two reimbursement rates and I would like to cut the hell out of the reuse ones. They have undue profits.

I am not against profits. Profits are great; but not at the expense of my blood and my body. When I go in there, I have to put my arm out to them and they put two large needles in there, and that's painful enough; and to know that I am not going to live my full life is painful enough.

But to know that they are going to poison me—what more do I have to say? I am sure you realize the dilemma that the patients are in and I appreciate your time and effort. I do.

Chairman HEINZ. Mr. Rosen, thank you. I think you have summarized it well.

Senator Pressler.

Senator PRESSLER. I join in the staff recommendations. I want to ask the panel for a brief comment on each of them.

First of all, recommendation No. 1, "* * * require the Department of Health and Human Services to conduct the necessary preclinical and clinical studies to determine whether reuse or disposable dialysis devices is safe and efficacious * * *." Well, I guess everybody would agree with that one.

"The DHHS," Department of Health and Human Services, "should withhold issuance of its proposal to establish lower confidence rates for dialysis services which assume reuse until the safety and efficacy of reuse is determined." I am sure everybody would agree with that.

Is that correct? These recommendations might be too mild, if you have more, please let us know.

Recommendation No. 3, "* * * the Department continue to allow individual physicians and clinics to decide whether or not to reuse. It should establish a two-tiered reimbursement system for dialysis facilities to reflect the difference in cost between the facilities that reuse devices and those that do not reuse. Such a system would allow Medicare to reduce payments to reusing facilities. It would not create undue pressure to reuse at clinics where physicians have decided reuse is unsafe or inappropriate for patients."

Would you agree with that?

Recommendation No. 4, "The Department regulations should be amended to include provisions that would require dialysis clinics to inform their patients in writing about potential risks * * *" and so forth.

There is one question I have about recommendations three and four. The equipment already says it is for single-use, only. We would have to change that, would we not?

You just had it there in your hand, John.

Chairman HEINZ. Yes. It says "For single use only."

Senator PRESSLER. We would have to change that, would we not?

Chairman HEINZ. To my mind, Senator, the key issue is the setting of standards for reuse if reuse is to take place. So that if a device is going to be reprocessed, it is reprocessed in a safe manner.

Second, an issue related to that which you have just touched on, is the issue of freedom of choice where an informed judgment needs to be made. Right now, as we have just heard, our witnesses have told us that they are not being informed of any of the risks; and, indeed, they are being told at the equivalent of medical gunpoint to "Hook up or shut up."

Senator PRESSLER. The next recommendation is that the FDA should "* * * adopt uniform Federal standards for the reprocessing and reuse of disposable dialysis devices in accordance with the provisions of the Food, Drug and Cosmetic Act."

What is your feeling about that? Do you think that there can be a way that these can be safely reused?

Go ahead, anybody; or should we say that none of them can be reused?

Mr. **Vogter**. Of course, you all know I am in favor of no reuse; but if the reuse question comes in and they can find out a good way to clean it, I would recommend a limit of the reuses—in other words, not unlimited. For instance, I would recommend no more than three reuses of the kidney.

For instance, say on Monday morning where we have a long time between dialyses, usually the patient has an overload of fluid. A new kidney is more readily taking off the overload of the fluid than a used one.

So if they come in Monday morning they should get a real good start of the week. Even if they have to use them the three times, it is like a compromise; but I prefer a new kidney every time.

Some doctors have brought up the question that they have what they call the new kidney syndrome. In other words, they say some people may feel sick, but they can have a choice. They can say, "OK, we will limit it three times for you," if that is the case.

Senator **Pressler**. So a recommendation that would go beyond what is in the report here is that if reuse is allowed that there be some limitation of two, three, or four reuses.

Mr. **Vogter**. Yes.

Senator **Pressler**. That is something that staff might look into.

Mr. **Vogter**. Also all the lines' which is very important. The blood lines' reuse because they fail. I forgot to mention when you asked me about it, also the blood lines develop tiny air holes in the lines and air, if it gets into your blood system, can be fatal. We have had cases where air is in the lines where they had to revive the patient with oxygen and did all kinds of emergency procedures.

So the rest of the patients just sit there with no guidance or nobody to help them. So this is very dangerous.

Dr. **Shuman**. May I say something, sir?

Senator **Pressler**. Yes. Go ahead.

Dr. **Shuman**. Generally, what we are speaking about here is taking some actions that would affect these companies where I think they are most vulnerable, which I think is in their profit structure.

I think that everyone in the Congress and in the Senate should be prepared to be deluged, if you tamper with these companies' present structure, with letters from their constituents who are on dialysis who have been pressured and manipulated by these companies into protesting anything that affects the profit structure of these companies because this has been done before and I think you should be prepared for it to happen again.

Senator **Pressler**. OK.

Do either of you have anything on the reuse or the recommendations of the staff which seek possible uniform Federal standards allowing reuse, or do you think we should not allow reuse at all?

Mr. **Rosen**. First of all, after I leave here today and I go back to my organization and my phones continue to ring off the hook with complaints about reuse and I tell them that we are starting to look into this, from today on we still have no standards. Obviously, I am not expecting any from this hearing.

But it is still unsafe; it is unproven; and it is being done right now while we are speaking. It is going to be done tomorrow and the next day.

I would like to address the issue of the label. The devices are manufactured under testing for one use only. They are not tested for multiple uses. They are not labeled as such.

There is no tensile test, no strength test. These units have decided to take it upon themselves to just reuse them at their whim. The manufacturer, who I have spoken to on many occasions, tells me that that label is his protection, that "We state to the physician, if you want to reuse it, it is on your head."

I am not looking for a lawsuit. I am just looking to be safe. That's all.

It is hard enough to be on dialysis. They are never going to change the label. The manufacturer will never change the label because they don't want the responsibility.

We are going to have to come up with someone in the Government, in the FDA or in Health and Human Services, who is going to have to say, "Yes, we are going to take this in our jurisdiction. We are going to control it and we are going to police it." That is the only way that it can be done.

With two reimbursement rates, as Dr. Shuman said, they are going to lobby like hell. They have spent millions of dollars in Pennsylvania to block a little informed consent bill that I tried to get passed in Pennsylvania. They just came in and bought so many lobbyists that no matter where I turned in Harrisburg there was a lobbyist there to follow me in the office; and I am just one man.

I am trying to speak for all of them and I feel that I am absolutely justified in what I am saying. Let me pay for my own dialyzer. Let me pay for my own lines. They say, "No, you are not allowed. Get the hell out. Go home."

When I first brought ~~it~~ up, I was told while laying on the machine with my blood in the machine, that if I open my mouth, "You have a wife and a daughter. You better watch out when she goes to school. You won't be there. You better shut your mouth."

That kind of abuse is disgusting.

Mr. **Vogter**. Sir?

Senator **Pressler**. Yes.

Mr. **Vogter**. Coming back to the standards—I am an engineer, that is why I think about these things—we should have some standards for quality control of the machines—the number of years they have been used and how effective the machines are—because many times when I was there two machines would break down simultaneously and that is devastating because the nurses cannot handle it.

For instance, say that we have one nurse for three patients, which means three machines. Now they have gone to one nurse for four machines. However, when the one nurse is on break or lunch, we have one nurse for eight machines; and when two machines break down simultaneously, she cannot handle it and she screams for help. Before help arrives, things are happening very quickly.

So we need the standards for the machines and also how many machines or patients a nurse can take care of. It is very important.

Senator PRESSLER. But those should be done by the Department of Health and Human Services at the Federal level, rather than depending on the States.

Mr. ROSEN. All right.

Senator PRESSLER. This is what these hearings are for: to get some recommendations on the table. I think that you witnesses have expanded on the six recommendations that the staff has very ably put forward.

If you think of more specific things that we should consider as a committee—and I presume we will be sending something over as a committee and taking some steps to establish an action program to solve this problem—please let us know.

Chairman HEINZ. I want to thank all four or our witnesses who have traveled with some difficulty considerable distances. I know it must be difficult in each and every one of your cases to tell your stories.

You are probably wondering what is going to happen when you get back to your friendly dialysis unit. I think you should have no fear of retribution.

If you do have any problems with your dialysis unit, please let me know directly. I will take whatever steps are necessary to see that you are properly treated with the respect that you deserve.

I think you have also been extraordinarily helpful to the committee. I think both Senator Pressler and I, thanks to your testimony, have a very clear understanding of exactly what the needs are.

You have been very specific and you have not minced your words, and you have been very reasonable as well in terms of what you think are the proper ways for your Government to proceed. Lest anybody neglect the point, I gather that all of you pay or have paid taxes to your Government, and all you expect in return is for your Government to accept and fulfill its responsibilities to you. So do we.

Again, thank you for your testimony.

Our second panel consists of three expert witnesses. I want to welcome at our witness table Dr. James R. Beall of Gaithersburg, MD. He is a toxicologist who has written several papers on toxicities of formaldehyde, including a paper on "Formaldehyde in Dialysis Patients;" Dr. Charles Wolf of Philadelphia, chief of the section on renal diseases at Pennsylvania Hospital and part owner of a for-profit dialysis clinic; and Dr. Terry Oberley, associate professor of pathology at the University of Wisconsin and a dialysis patient himself.

Gentlemen, on behalf of the committee, I want to thank you for assisting us in understanding and appreciating the potential risks of reusing these disposable devices. Each of you has provided written statements, which will be made a part of the record. Let me begin with Dr. Beall. Would you please proceed.

STATEMENT OF JAMES R. BEALL, PH.D., BOARD-CERTIFIED TOXICOLOGIST, GAITHERSBURG, MD

Dr. **Beall**. First of all, I guess I should make clear that while I am a Federal employee and have been for some time the statements that I present today are my own opinions as an expert on formaldehyde toxicity.

Chairman **Heinz**. I want to apologize. I may be mispronouncing your name. Is it Beall or Bell?

Dr. **Beall**. It is Beall sir.

Chairman **Heinz**. As you may be aware, for many years Maryland had a Senator Glenn Beall, who spelled his name exactly the same way as you did and I mispronounced it his entire life. [Laughter.]

Dr. **Beall**. Well, there is some indication that the families may be the same, but have attempted to disown each other over the years.

Senator, committee members, my name is James Beall. I obtained a doctor of philosophy degree in physiology from the University of Oklahoma Medical Center in 1970 and I am board certified in toxicology and currently am president of the Association of Government Toxicologists, a scientific association whose membership is drawn exclusively from senior toxicologists in the Federal Government.

As part of my professional experience both as a Federal employee and as a private citizen and consultant, I have investigated the toxicity of formaldehyde, including the use of formaldehyde in dialyzers. Copies of articles that I have published and my CV have been made available to your staff.

If dialysis patients in the United States are to receive the highest quality medical care at the lowest cost, we must address serious questions concerning safety and efficacy in the reuse of disposable equipment. Answers to these questions will involve defining and balancing the benefits and the risks that are attendant with the use of new as well as reused disposable products in dialysis therapy.

In the last 20 years, formaldehyde has become the most widely-used sterilant in the reuse of dialyzers. For this reason my statement focuses on formaldehyde in reuse.

That formaldehyde is highly toxic under certain circumstances has been known since 1905. In the last 10 years, information about the toxic and carcinogenic potential of formaldehyde indoors resulted in widespread public concern about exposure to it in the atmosphere.

Residual formaldehyde is present in dialyzers when they are reused and, in this manner, patients may be exposed to concentrations of formaldehyde during therapy that exceed that to which humans are exposed by way of the atmosphere. Direct exposure to formaldehyde during dialysis therapy has been reported to reach levels exceeding 100 parts per million and is commonly around 5 parts per million.

Such patients are placed at risk by formaldehyde's toxicity, and yet for a number of reasons relatively little attention has been given to the toxicological issues involved in dialysis even though patients may be exposed directly to formaldehyde and other toxic chemicals during therapy.

Some research on formaldehyde toxicity in dialysis patients has been done in an attempt to understand if exposure to it during therapy results in adverse effects. The results indicate that significant quantities of residual formaldehyde following a resterilization procedure may enter the patient during dialysis and that that exposure is associated with such effects as burning at the site of entry, possibly cytogenetic and hepatic damage, eosinophilia, hypersensitivity, antibody formation and even death.

Studies that have been reported can be classified into roughly three categories: clinical reports, hematological analyses, and sterilization procedures and results. Clinical observations of patients usually report acute reactions. They may range from mild and reversible to, as mentioned previously, fatal.

Hematological research has frequently been directed at describing and understanding immunological changes caused by exposure of red blood cells to formaldehyde. Such studies have shown that dialysis patients develop antiformaldehyde antibodies and anti-N-like antibodies in response to changes in their own red blood cells caused by residual formaldehyde in reused dialyzers.

Recent research shows that formaldehyde may cause other immunological changes in dialysis patients as well.

As far back as 1959 Timmis and others showed that formaldehyde may inhibit the anticoagulant effects of heparin. Such an action would tend to increase the formation of blood clots and may necessitate the use of larger-than-usual doses of heparin in dialysis patients.

Collectively, the studies have shown that a variety of significant changes occur in patients as a result of their exposure to formaldehyde. Because those changes occur, procedures for sterilizing and reusing dialyzers have been evaluated and reported.

However, a single best method, if one exists, has yet to be properly evaluated in clinical tests or accepted into general use. This is not to imply that there have not been attempts to standardize reuse procedures. Panels of experts over the years have made several serious attempts to standardize the procedures.

For example, a study supported by NIH in June 1981, which was never completed, was an attempt to standardize the process. Much of the research in that study indicated that sterilization might be appropriate. But one of its conclusions states that "The clinical experience does not provide the information that could appropriately lead to a standardized protocol * * *."

In June 1982, the Executive Committee of the National Kidney Foundation also attempted to derive standardized procedures. In August 1985, the Association for the Advancement of Medical Instrumentation proposed recommended practices for the reuse of hemodialyzers.

This panel report offered suggestions to be followed by physicians and others involved in the reuse of dialyzers. But, no epidemiological or clinical studies were presented to substantiate that the procedures suggested do, in fact, produce safe and effective equipment. Instead, the report relies to a significant degree on the three reports that I mentioned just a while ago, none of which contain controlled prospective studies to establish the safety and efficacy of reuse.

Dialysis is life-saving therapy. However, like most treatment, it entails risk. The research to date has demonstrated that important risks are associated with the sterilization and reuse of dialyzers. However, it has not established whether the sterilization and the reuse of dialyzers and other disposable equipment produce significant hazards in subsequent use or whether they result in therapy that is as safe and efficacious as is the single-use of new dialyzers.

What is lacking? There is a notable lack of epidemiological and clinical research in this area. To the best of my knowledge, there has not been one well-designed prospective study with sufficient power to address questions about the safety and efficacy of sterilization and the reuse of disposable dialyzers and associated equipment.

Until the risks of dialyzer reuse are defined, decisions concerning reuse are at best educated guesses and, at worst, wrong. Without this critical research, dialysis patients have little hope of receiving the highest quality medical care at the lowest cost.

Thank you.

Chairman HEINZ. Dr. Beall, thank you very, very much for a very careful summarization of the research and its conclusions or, unfortunately, lack of conclusions in much of the research.

[The prepared statement of Dr. Beall follows:]

TESTIMONY OF DR. JAMES R. BEALL

CONCERNING FORMALDEHYDE AND DIALYSIS

My name is James R. Beall. I obtained a Bachelor of Science degree in natural science from Oklahoma State University in 1963, a Master of Science degree and a Doctor of Philosophy degree in physiology from the University of Oklahoma, Medical Center in 1965 and 1970, respectively. I am certified in general toxicology by the American Board of Toxicology, Inc.. I either serve or have served on the Board of Directors of several health related corporations, including the American Board of Toxicology, Inc., and the Toxicology Laboratory Accreditation Board, Inc. both of which are not-for-profit corporations engaged in setting standards for the practice of toxicology. I am President of the Association of Government Toxicologists, Inc., a scientific association whose membership is drawn exclusively from senior toxicologists in the Federal Government.

Prior to joining the government, I was senior toxicologist and section leader for Schering Corporation, a manufacturer of pharmaceuticals. There I designed and conducted toxicological studies on drugs, and evaluated health data to determine the potential risk of exposing humans to toxic chemicals. I also participated in designing clinical studies for evaluating the effects of pharmaceuticals in human subjects.

Since 1977, I have been an employee of the United States Government, and have served as a senior level scientist in the Environmental Protection Agency and in the Occupational Safety and Health Administration. I am now with the Department of Energy. In each of these positions, I have evaluated the toxicological potential of chemicals and managed research to address toxicological problems. My assignments included serving as a United States representative to various expert workgroups on toxicology in the Organization of Economic Cooperation and Development. At the request of other agencies, I served on the Consumer Product Safety Commission's Federal Panel on Formaldehyde and as a Panel Member in the Consensus Workshop on Formaldehyde.

During my professional career, I have written several scientific articles and reports, and given many presentations and public speeches on the toxicity of a variety of chemicals. As a private consultant, I have, when appropriate, provided advice regarding toxicology to clients, including, some with an interest in formaldehyde toxicity and hemodialysis. As part of these experiences, both as a Federal employee and as a private citizen, I investigated the toxicity of formaldehyde and wrote articles on the topic. The activities included investigating the use of formaldehyde in the reuse of dialyzers and writing a recently published scientific article on that topic.

A copy of my C.V., attached, contains greater detail about those and other educational and professional experiences.

DIALYZER REUSE

If dialysis patients in the United States are to receive the highest quality medical care at the lowest cost, we must address serious questions concerning safety and efficacy in the reuse of disposable equipment. These questions cover diverse areas and issues such as economics, informed consent and toxicity. In this nation, there are over 75,000 patients undergoing regular dialysis. If one considers the patients' lost time from work and the expenses of therapy, education, and all other activities associated with dialysis, the annual cost of such care to the patients, to the medical care community and to society totals billions of dollars. Direct cost to the Federal Government alone exceeds 1.5 billion dollars per year. In an increasing attempt to reduce the cost of dialysis at therapy centers, more and more patients are being dialyzed with systems that incorporate reused disposable equipment, including dialyzers. Such reuse occurs even though the equipment was designed and manufactured to be used only once before disposal. Answers to questions of safety and efficacy involve defining and balancing the benefits and risks that are attendant with the use of new as well as reused disposable products in dialysis therapy.

There are many procedures for the resterilization of disposable dialyzer equipment. In the last 20 years, formaldehyde has become the most widely used sterilant for the reuse of dialyzers. Its use has grown with increasing numbers of patients on dialysis and with economic pressure to reduce therapy costs. For this reason, my statement focuses on formaldehyde and the reuse of dialyzers.

That formaldehyde is highly toxic under certain circumstances has been know since 1905. In the last 10 years, information about the toxic and carcinogenic potential of formaldehyde indoors resulted in widespread public concern about exposure to it in the atmosphere, and in regulatory actions by various State and Federal authorities. Three colleagues and I wrote an article in 1984 that summarizes many health effects of formaldehyde and some of these actions (1, copy appended). Residual formaldehyde is often present in dialyzers when they are reused. In this manner, patients may be exposed to concentrations of formaldehyde during therapy that exceed that to which humans are exposed via the atmosphere. Direct exposure to formaldehyde during therapy has been reported to reach levels exceeding 100 ppm and is commonly around 5.0 ppm. Such patients are placed at risk by formaldehyde's toxicity (2). Yet, for a number of reasons, relatively little attention has been given to the toxicological issues involved in dialysis, even though patients may be exposed directly to formaldehyde and other toxic chemicals during therapy.

Some research on formaldehyde toxicity in dialysis patients has been done in an attempt to understand if exposure to it results in adverse effects in them. The results indicate that significant quantities of residual formaldehyde following a resterilization procedure may enter the patient during dialysis and that the exposure is associated with a variety of adverse effects. Such effects include burning at the site of entry, possible cytogenetic and hepatic damage, eosinophilia, hypersensitivity, antibody formation, and even death. Because many of the adverse effects are described in two of my review articles (2,3 copies appended), I need not discuss them in detail at this time. It may, however, be useful to summarize categories of studies that have been reported.

Studies that have been reported could be classified into roughly three categories: clinical reports, hematological analyses, and sterilization procedures and results. Clinical observations of patients and occurrences of adverse reactions have been reported by many physicians and health workers who are associated with dialysis. They usually report acute reactions in patients that range from mild and reversible to fatal. In some instances the reports establish the cause, in others they do not. Clinical reports may raise questions about the toxic potential of using formaldehyde in resterilization, but because of their nature they are rarely conclusive.

Hematological research has frequently been directed at describing and understanding immunological changes caused by the exposure of red blood cells to formaldehyde. Such studies have shown that many dialysis patients develop Anti-formaldehyde antibodies and Anti-N-like antibodies in response to changes in their own red blood cells caused by residual formaldehyde in reused dialyzers. Recent research shows that formaldehyde may cause other immunological changes in dialysis patients. For example, they may develop antibodies to serum albumin-formaldehyde conjugate (4). In 1959, Timmis, et al. showed that formaldehyde may inhibit the anticoagulant effects of heparin. Such an action would tend to increase the formation of blood clots and may necessitate the use of larger than usual doses of heparin in dialysis patients (5). Their work has been confirmed by others. Collectively, these studies show that a variety of significant changes occur in patients as a result of their exposure to formaldehyde in reused filters.

Because these changes occur, numerous procedures for sterilizing and reusing dialyzers have been reported and evaluated. These reports often describe the characteristics of residual formaldehyde, show rinsing rates and times, and explore the efficacy and value of various sterilization techniques. The sterilization procedures are generally the ones that are in current use by the group reporting the data. A single best method, if one exists, has yet to be properly evaluated in clinical tests and accepted into general use. This is not to imply that there haven't been attempts to standardize reuse procedures.

Panels of experts have made several serious attempts to standardize procedures for reusing dialyzers. A few examples may illustrate the limitations of these attempts.

In June 1981, the National Nephrology Foundation (NNF) issued a report to the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDKD) on the multiple use of dialyzers (6). The study, which was in partial fulfillment of a contract with NIADDKD, was to develop conclusions regarding the safety and efficacy of procedures that are employed in the multiple use of hemodialyzers. The study included a survey of the literature on the topic and testing a variety of procedures involved in the function, disinfection, and cleaning of dialyzers that had been stored for repeated use. Much of the research was done under subcontract, none of it was confirmed by appropriate clinical trials. Indeed, this report concludes that, "..The clinical experience does not provide information which could appropriately lead to a standardized protocol for dialyzers with suitable quality control and process control. There is no published prospective randomized clinical trial which confirms the satisfactory clinical experience."(6).

In 1981, Arthur D. Little, Inc. under subcontract to the National Nephrology Foundation, Inc. issued a final report in support of the NNF contract mentioned above (7). Under this subcontract, a literature review and a combined program of physical tests on dialyzers and in vitro research was done. It included conducting a number of in vitro experiments to address several important issues in the sterilization and reuse of dialyzers. After reviewing the literature and conducting the research, Arthur D. Little stated, "Any clinical implications of the results of the combined program must, of course, be confirmed by appropriately controlled clinical trial before implementation." (7).

In June 1982, the Executive Committee of the National Kidney Foundation (NKF) convened a group of physicians, nurses, patients, industry representatives, and microbiologists to formulate standards of the reuse of hemodialyzers (8). These NKF "standards" suggest that each facility which practices reuse of dialyzers should develop specific written procedures concerning all elements of reuse. It states, "These aspects of reuse are appropriately individualized to the particular facility, but should be directed to achieve an effective, safe, system, and a uniform product." The NKF document offers no advice on how to conduct follow-up evaluations to determine if, in fact, the written procedures or the use of the standards produced "An effective, safe, system" or uniform reusable products. The document presented no epidemiological data or controlled clinical studies to demonstrate that the standards suggested were capable of producing reused products that were safe and effective.

In August 1985, the Association for the Advancement of Medical Instrumentation proposed recommended practices for the reuse of hemodialyzers (9). This panel report offers suggestions to be followed by physicians and others involved in the reuse of dialyzers. No epidemiological or clinical studies are presented to substantiate that the procedures suggested do, in-fact, produce safe and effective equipment. Instead, this report relies to a significant extent on the three reports mentioned above, none of which contained controlled prospective studies to establish the safety or efficacy of reuse.

Dialysis is life saving therapy. However, like most treatments it entails risk. The research to date has demonstrated that important risks are associated with the sterilization and reuse of dialyzers. However, it has not established whether sterilization and reuse of dialyzers (and other disposable equipment) produce a significant hazard in subsequent use, or whether they result in therapy that is as safe and efficacious as is the single use of new dialyzers.

What is lacking? Answers to the questions of risks of dialyzer reuse require additional research. There are studies which should be done soon to reduce as quickly as possible the number of patients who are at risk. The research to date has been done largely on an ad hoc basis. While clinical observations, hematological studies, in vitro studies, and literature reviews have been reported, there is a notable lack of epidemiological and clinical research.

To the best of my knowledge, there has not been one well-designed prospective study with sufficient power to address questions about the safety and efficacy of sterilization and reuse of disposable dialyzers (and associated equipment). Much research is needed to answer questions of efficacy and safety of dialyzer reuse; it includes conducting proper prospective studies involving clinical trials. Such studies are needed to examine dialyzer use and reuse, standardized sterilization procedures, patient reactions, clinical chemistry, and a variety of other endpoints. Many scientists who have looked at this question have come to the same conclusion. For example, in 1978, a collaborative study by several agencies of the Federal Government was undertaken to evaluate dialyzer reuse and address questions of safety and economy. That project had several objectives; it included conducting appropriate clinical trials to evaluate various dialyzers and reuse procedures. Unfortunately, it was was stopped prematurely, before the clinical trials were initiated. They remain to be done.

Until the risks of dialyzer reuse are defined, decisions concerning reuse are at best educated guesses and at worst, wrong. Without this critical research, dialysis patients have little hope of receiving the highest quality medical care, at the lowest cost.

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Additional attachments to Dr. Beall's testimony included in appendix.

December 1985

CURRICULUM VITAE

James Robert Beall

Date of Birth: June 29, 1940

Education:

1954-1958	Stillwater High School
1958-1959	Oklahoma State University
1959-1960	Amarillo College
1960-1961	Texas Technological College
1961-1963	Oklahoma State University
1963-1970	University of Oklahoma (in affiliation with Brown University; Providence, Rhode Island)

Degrees:

A.A.S.	1960	Amarillo College (Major-Business)
B.S.	1963	Oklahoma State University (Major-Natural Sci.)
M.S.	1965	University of Oklahoma (Major-Physiology)
Ph.D.	1970	University of Oklahoma (Major-Physiology, Minor-Biochemistry)

Certifications:

1980-Present	Certified in General Toxicology by the American Board of Toxicology, Inc. Recertified 1985.

Professional Experience:

3/85-8/85	Senior Policy Advisor, International Affairs
3/80-Present	Senior Toxicologist, Research Manager Office of Energy Research, Health Effects Research Division, U.S. Department of Energy
2/79-2/80	Special Assistant (Toxicology), U.S. Occupational Safety and Health Administration
4/78-Present	United States Representative to various Expert Workgroups on Toxicology of the Organization of Economic Cooperation and Development
8/77-2/79	Biological Sciences Administrator, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.
1975-1977	Section Leader, Large Animal Toxicology and Teratology, Department of Toxicology and Pathology, Schering Corporation, Lafayette, New Jersey

Professional Experience: (cont'd.)

1972-1975	Principal Scientist in Toxicology, Schering Corporation, Lafayette, New Jersey
1969-1972	Senior Scientist, Teratology, Schering Corporation, Lafayette, New Jersey
1966-1969	Research Assistant, Institute for Health Sciences, Brown University
1963-1966	Research Assistant, Department of Gynecology and Obstetrics, University of Oklahoma Medical Center

Qualified Expert Witness (Federal District Courts):

-Toxicology and Chemistry

Consultantships:

-Science Applications, Inc
-Pharmacopathics, Inc.
-Litton Bionetics, Inc.
-Over 25 Legal Associations, including:

Vickery and Webb; Houston, Texas
Lafond and Evangelisti; Denver, Colorado
Roberts and Shefelman; Seattle, Washington
Pippin, Bocci, and Shinn; Portland, Oregon
Boothe, Prichard, and Dudley; Fairfax, Virginia

Professional Activities:

1985-	Co-Chaired, symposium "Some Pragmatics of Exposure and Health"
1985-	Expert Testimony, ~~State~~ Federal Court, Spokane WA
1984-	Member, Interagency Risk Management Council, Subgroup on Formaldehyde, White House, Office of Science and Technology Policy, Office of the President
1984-	Expert Testimony, State Court, Yakima, WA
1983-Present	Chairman, Board of Directors, Association of Government Toxicologists
1983-1985	United States Representative to Expert Workgroups, Existing Chemicals Program of the Organization of Economic Cooperation and Development (by appointment)
1983	Chairman, Nominations Committee, Soc. Toxicology, Subsection on Reproduction and Developmental Toxicology
1983	Member, Consensus Panel on Formaldehyde, White House, Office of Science and Technology Policy, Office of the President
1983	Expert Testimony, Federal District Court, Dallas, TX
1983-Present	Member, Board of Directors, Toxicology Laboratory Accreditation Board, Inc. (elected)
1982	Expert Testimony, Federal District Court, Denver, CO

1981-1983	Executive Officer-Secretary (elected), American Board of Toxicology, Inc.
1981-1985	Member, Board of Directors, American Board of Toxicology, Inc. (elected)
1980-1982	United States Representative, Updating Panel on Toxicity Testing, Organization of Economic Cooperation and Development (by appointment)
1980	Member, Federal Panel on Formaldehyde, Consumer Product Safety Commission and the National Toxicology Program
1980-Present	Member, Federal Interagency Workgroup on Indoor Air Quality
1980	Member, IRLG Workgroup on Formaldehyde
1980	Member, NIEHS Workshop on Research Needs in Reproductive Toxicology
1980	Member, Program Committee for the Teratology Society
1980-1983	Member, Public Affairs Committee of the Teratology Society
1979	Member, IRLG Workgroup on Benzidine Dyes
1978-1981	United States Representative to Expert Groups on Toxicity Testing of the Organization of Economic Cooperation and Development (by appointment)
1978	Member, NIH Workshop on Effects on Environmental Stress in Carcinogenic Testing
1977-1978	Chairman, EPA Workgroup for Development of Testing Rules under Section 4 of TSCA
1977	Member, Workshop on "Training Scientists for Future Toxic Substances Problems," Annapolis, Maryland
1977	Chaired public meeting on "Interagency Liaison Work Group on Testing Standards and Guidelines", Environmental Protection Agency, Washington, D.C.
1977-1978	Alternate Member, TSCA Interagency Testing Committee (by appointment)
1973	CEO, Mid-Atlantic Reproduction and Teratology Association
1972	Chairman, Workshop on Test Methods in Teratology, Mid-Atlantic Reproductive and Teratology Association
1971-1977	Member, Pharmaceutical Manufacturing Association, Subcommittee on the Safety Testing of Drugs in Neonates
1971-1975	Member, Steering Committee for the Mid-Atlantic Reproduction and Teratology Association

Societies:

-Past or Present Member of:

American Association for the Advancement of Science
American Chemical Society
American College of Toxicology
American Physiological Society
American Teratology Society
Association of Government Toxicologists
Environmental Mutagen Society
European Teratology Society
Mid-Atlantic Reproduction and Teratology Association
New York Academy of Sciences
Society of Toxicology

Honors:

-Delta Sigma Pi
-Sigma Xi

-Listed, American Men and Women of Science, 15th Edition (Medical and Biological Sciences)
-Listed, Who's Who in Washington, Positions and Leadership in the Nation's Capital, 1983-1984

-Award of Appreciation, Consumer Product Safety Commission, 1980
-Certificate of Appreciation, Department of Energy, 1980
-Award of Appreciation, American Board of Toxicology, 1985

Numerous Public Speeches and Scientific Presentations:
-Listed, Sigma Xi Regional Lectureship Program, Mid-Alantic Region

Publications and Reports:

-Over 150 confidential toxicology studies, conducted and reported to regulatory agencies throughout the world.

-Scientific Articles, Chapters, Abstracts, Editorials, letters. (attached lists show publications)

December 1985

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Chairman HEINZ. Dr. Wolf.

Again, I note I have the pleasure to introduce another Pennsylvanian. I don't think there was any intent to load this hearing with Pennsylvanians; it is just that we have a lot of talent in Pennsylvania.

STATEMENT OF DR. CHARLES J. WOLF, HEAD, SECTION ON RENAL DISEASES, PENNSYLVANIA HOSPITAL, PHILADELPHIA, PA

Dr. WOLF. We are also pretty close. First of all, let me say that I am often put in the position of giving a balanced view here. I hope I don't offend any of the dialysis patients, and I also hope I don't offend my fellow nephrologists who do reuse. I will try to be fair to both sides.

I am the co-medical director and part owner of an outpatient for-profit dialysis facility which currently has 60 hemodialysis patients treated at the facility and 20 patients treated with peritoneal dialysis at home. We currently do not reuse any disposable equipment.

I have been asked to address the Committee on three aspects of hemodialysis reuse. First, is reuse safe? Second, is informed consent necessary and desirable? Third, should there be uniform Federal standards?

The first question: Is reuse safe? Let me state that I am not in the least opposed to the concept of reuse. It is quite possible that reuse is every bit as safe as single-use, perhaps even more safe. The problem is that we simply do not know.

There has never been a controlled prospective clinical study comparing the use of new versus reused hemodialyzers. Compare this with the current NIH-sponsored investigation the efficacy of a treatment called plasmapheresis for kidney diseases caused by systemic lupus erythematosus.

The lupus study is multi-centered, clinically based and properly blinded so that individual investigators' biases are shielded from the interpretation of the study. By contrast, the only NIH-funded study which addresses the methodology involved in reprocessing dialyzers, the so-called Dean report, does not contain a clinical component. Although a clinical arm of the study was called for in the original proposal, it was not delivered.

Even if one accepts the results of the Dean report, it is at best a laboratory comparison of various methods for cleaning and reprocessing dialyzers.

Clinical studies of dialyzer reuse are uncontrolled and, for the most part, have been conducted by those who are intent on proving the safety of reuse. At best, these studies claim short-term safety and efficacy equivalent to first-use. At worst, claims are made which cannot be substantiated even in the context of the study's own data. Such is the case with the Dean report in my opinion.

In the absence of adequate data, then, we are left with the question of ethics. Most ethical systems handle this type of problem under the uncertainty principle. This principle states, quite simply, that if you are not sure whether an action is right or wrong, you should not do it.

No one disputes that reuse would not be practiced as widely today if it cost as much as, or more than, single-use. While dialyzer reuse had its origins in the necessity to rebuild and sterilize the earliest artificial kidneys on site—such as the Kiil dialyzer—this practice has continued in the modern era of readily available, economically priced, single-use dialyzers only for economic advantage.

Dialysis providers, therefore, are being asked to embrace reuse not out of concern for the health of the dialysis patients, but for the financial health of their units and perhaps even of the Health Care Financing Administration itself. Certainly if reuse were proven safe, it could be mandated by HCFA directly or indirectly through a reduction in reimbursement rates.

If left unproven, as we now have it, those of us who support the uncertainty principle will continue to have a great deal of uncertainty to support.

The second question: Should there be informed consent? The answer to this is certainly yes; however, and as we have heard this morning, the implementation of informed consent and the absence of coercion in this circumstance is problematic.

For example, if I advise a patient on the merits of home peritoneal dialysis versus standard hemodialysis and if the advantages and disadvantages of each method are presented fairly to this person and to his family, and if this person is free to choose either method solely on the basis of these factors, we have a basis for a reasonable informed consent contract. The person involved can weigh the advantages and disadvantages of either choice, and make a decision.

Alternatively, he or she may ask me to make the decision, which I can do in conscience after explaining the factors elaborated above.

How may I transfer this principle to the reuse of dialyzers? First of all, as stated in my first answer to the question on safety, I have no good clinical data upon which to base my discussion.

The person can only choose to accept the reused kidney and save the center—certainly not himself—some money, or demand a new kidney with each use. In that circumstance why would anyone choose reuse except for that small percentage of patients who experience some adverse reactions with first-use syndrome? What other compromises might be employed?

He could agree to reuse kidneys in this center or go somewhere else. Where else would a patient go?

Many centers are already overutilized. In the city of Philadelphia, for instance, most centers are running at 150 percent of capacity. If a patient called me today requesting a transfer from a center which practices reuse to my center—this occurs quite frequently—I could not accommodate him.

What other compromises? Should a center that reuses publish its criteria for reuse, thereby informing the patients of minimal standards for the practice of reuse in that unit? Should the center invite the patient to join in the policing of these standards? This is reasonable if there were some sort of uniform standards.

This brings us to the last question. Should there be Federal guidelines for reuse?

The answer to this question again, in my view, is yes. There have been several reasonable standards published for reuse of dialyzers.

California has adopted a set of mandatory standards which assures at least the short-term efficacy and safety of dialyzer reuse. The National Kidney Foundation has published voluntary standards which are less specific and less stringent, but nonetheless serve to address the problem of reuse in light of the current knowledge and state-of-the-art technology.

These standards contrast starkly to States such as Pennsylvania which have no reuse legislation and where kidneys are reused as many as 40 or 50 times in some centers.

In the absence of uniform standards compiled by a multidisciplinary committee, proposals for such standards become progressively more arbitrary, more political and less scientific. This can threaten the entire practice of dialysis.

As an example, I will read to you in part, without comment, a copy of a recent proposal for reuse legislation before the Pennsylvania State Legislature. This is Pennsylvania Senate bill No. 1154, October 1985:

> Section A: The General Assembly finds that providers of kidney dialysis services in the Commonwealth increasingly require patients to reuse single-use dialyzers. Medical evidence conflicts as to the health effects of dialyzer reuse. No Federal or state standards for safety and performance for reprocessing the dialyzers exists.
>
> Section B: The General Assembly further finds that the data regarding the reuse of single-use hemodialyzers by patients and facilities in the Commonwealth is insufficient to determine appropriate action in this issue.
>
> Section C: The General Assembly thereby directs the Department of Health to collect data relating to the use of new and reused dialysis filters.
>
> Section D: The Department shall make a report to the General Assembly, including a summary of data collected, and an analysis of the following issues: legal liability of reuse, cost containment, health effects, risk/benefit ratios, performance of new versus reused dialyzers, occupational health problems to employees, and the need for the state to adopt standards.
>
> Section E: No facility providing kidney dialysis to patients shall be reimbursed by the Department unless each invoice submitted to the Department shall certify that a new dialyzer was used in each dialysis treatment.

End of Senate bill 1154.

In conclusion, the practical way to answer these three questions, in my mind, is in reverse order. The modern-day proponents of reuse claim that the practice is not inherently evil just because it is done to save money any more than the earliest reuse was good because it was done out of necessity. They may well be correct.

However, we have an obligation in the meantime to protect the rights of the hemodialysis patients, whose very lives depend on the quality of the dialysis treatments they are given, until this issue is settled.

A set of uniform Federal guidelines agreed upon by a multidisciplinary committee—including physicians and nurse clinicians, basic scientists and patient advocate groups—would be a first step in assuring the safety in light of our present-day knowledge.

Second, some sort of equitable informed-consent policy, including freedom of choice, should be made part of these Federal guidelines.

Finally, a federally mandated controlled prospective study looking at the practice of reusing dialyzers should be organized. If Medicare and other third-party payers can rightfully withhold reimbursement for procedures such as plasmapheresis until they are of proven efficacy, it is reasonable to expect that the question of dialyzer reuse—a major part of the end-stage renal disease program, which has already cost billions of dollars—can be scrutinized.

Ironically, if strict Federal guidelines are approved but a reuse study is not mandated, the question may never be answered. The cost of buying a new dialyzer is decreasing every year while personnel costs, which are a major component of reuse systems, are increasing.

It is quite possible that the costs of reprocessing a dialyzer in compliance with strict standards may become so high as to preclude any savings whatsoever. In that case, the reused dialyzer, even if it is a better device, may disappear.

Thank you.

Chairman HEINZ. Thank you very, very much, Dr. Wolf.

Dr. Oberley.

STATEMENT OF DR. TERRY OBERLEY, ASSOCIATE PROFESSOR OF PATHOLOGY, UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON, WI

Dr. OBERLEY. Thank you for inviting me here. I have submitted a statement to the committee. I would like to just briefly summarize what that statement says.

Chairman HEINZ. Very well, and your entire statement will be part of the record, Dr. Oberley.

Dr. OBERLEY. I have been concerned about the safety of the reuse of dialyzers for a number of years. This concern developed because of anecdotal accounts by dialysis patients who were experiencing physical difficulties when dialyzers were used in their treatments whereas, previously, they had been feeling well on dialysis.

I have, therefore, spent some time searching the literature for documentation on the problems associated with the reuse of dialyzers. These problems can be divided into two major categories.

No. 1, those associated with loss of dialyzer efficiency; and, No. 2, those associated with the use of formaldehyde for reprocessing dialyzers.

The loss of dialyzer efficiency with reuse is well known. It should be the goal of every nephrologist taking care of dialysis patients to dialyze as efficiently as possible. It is, in fact, efficient dialysis which I feel has led to my remarkable success as a dialysis patient.

I have been on dialysis for 13½ years and have been hospitalized for 4 days.

I feel that the process of extensively reusing dialyzers is providing less than optimal care. The long-term consequences are, in fact, going to be increasing costs rather than reduction since patients who are less than optimally dialyzed are going to have serious health side effects.

The second important consequence of reuse is the side effects of using formaldehyde as a sterilizing agent. First, it is not known what an optimal level of formaldehyde is for adequate sterilization. The consequences of this are contamination and this leads to bacterial infection.

Second, formaldehyde has severe acute side effects, including hemolytic and autoimmune diseases including anaphylaxis.

Finally, formaldehyde itself is a very potent compound which has mutagenic and carcinogenic effects.

Because of these concerns with their use, I feel a number of steps should be taken to resolve some of the problems. First, I must mention that I will continue to refuse to reuse dialyzers because I feel the loss of efficiency will seriously impair my functioning as a full-time pathologist and researcher.

However, for those who are forced to reuse, I would advocate the installation of informed consent with freedom of choice. I would think a study should be performed to determine the optimal number of times a dialyzer may be safely reused.

We must seek alternate ways to sterilize dialyzers to avoid the use of formaldehyde. If formaldehyde must be used, we must establish a safe level below which toxicity will not occur and we need a grievance mechanism to protect patients who are not being adequately dialyzed because of reuse.

In summary, I feel that reuse can be safe only if we develop standards for safer use, and this includes most importantly the number of times that a dialyzer may be reused, and a safe way to sterilize dialyzers. I should mention that research is being conducted on alternate ways to sterilize dialyzers and I am convinced that many of these ways are, in fact, safe.

Thank you.

Chairman **Heinz**. Dr. Oberley, thank you very much.

[The prepared statement of Dr. Oberley follows:]

STATEMENT OF TERRY D. OBERLEY, M.D.

This letter is to state my position on the reuse of dialyzers during kidney dialysis. The first question of interest is whether this procedure is safe and efficacious. It is known, in fact, that there are a number of side effects from reuse. Some of these are side effects of the formaldehyde used in sterilization. These include acute hemolysis and anti-N antibodies. There are also side effects of the reuse process. These include contamination and loss of dialyzer efficiency. Contamination has been a serious problem in some dialysis units since the "safe" level of formaldehyde required for sterilization is not known; in at least one dialysis unit patients died from the use of contaminated reused dialyzers. The number of side effects and the consequences of reuse of dialyzers has never been adequately studied in a controlled clinical situation. Concerning formaldehyde side effects, the acute effects would be relatively easy to demonstrate by comparing patients who reuse versus those who do not reuse. However, assessing the effects of dialyzer reuse is much more difficult since we do not have good biochemical and physiological parameters to determine the adequacy of dialysis. It is well known from the literature that with increasing dialyzer reuse, the efficiency of the dialysis goes down, and therefore certainly there reaches a point at which optimal efficiency is not obtained. I would think that the number one goal of any physician treating a dialysis patient would be to make the dialysis process as efficient as possible.

I am most concerned in the whole issue of dialyzer reuse with the role of formaldehyde as a sterilizer. In fact, it is well known from laboratory studies that formaldehyde is a carcinogen in laboratory animals (references include Cancer Research, Vol. 43, pp. 4382-4392, 1983; Toxicology, Vol. 24, pp. 9-14, 1982; Gann, Japanese Journal of Cancer Research, Vol. 45, p. 451, 1984; and Cancer Research, Vol. 40, pp. 3390-3402, 1980). As a member of the Toxicology Research Center of the University of Wisconsin, I have been trained in the basic principles of toxicology and know several important facts about chemical carcinogenesis. These include: (1) The intrinsic carcinogenicity of a chemical does not depend on dose level, although the proportion of animals developing cancers at the earliest time that tumors are detected are usually related to dosage. (2) Metabolic studies have shown that most differences between humans and experimental animals are quantitative rather than qualitative and support the idea that animal results can be used to predict human responses. (3) Exposure to any amount of carcinogen, however small, must be regarded as an addition to the total carcinogenic risk. (4) There is a time lag between exposure and appearance of cancer. These facts demonstrate that formaldehyde is a potential risk in dialysis patients. Unfortunately, they also demonstrate the chief problem with the area of assessing formaldehyde risk in dialysis patients. That is, it requires a long period of time between exposure and subsequent development of overt disease. Therefore, most nephrologist will say that formaldehyde reuse is safe since, over the short run, it is relatively safe.

This, of course, does not take into account those patients who develop allergic responses.

It is most peculiar in light of the serious carcinogenic potential of formaldehyde that this compound has not been banished in the United States. This issue has been addressed recently in Science magazine, (Vol. 216:1285-1291, 1982). This article mentions that most broad based scientific panels have established the following principles: (1) Confirmed positive animal data are presumptive evidence of carcinogenicity in humans. (2) With current information and methods, it is not possible to establish thresholds or no effect levels that can be reliably applied to the human population. (3) Positive human epidemiologic data are not necessary to conclude that a chemical substance poses a significant human risk. These principles are consistent with the accepted scientific policy that it is preferable to err on the side of caution in interpreting the available scientific data in order to avoid failure to regulate a serious health hazard. What these principles mean is that there is no evidence demonstrating that there is a dose level below which it is certain that formaldehyde will not cause cancer. (Reference: Federal Register, Vol. 46, pp. 11188, 1981).

The potential risks of cancer to dialysis patients exposed to formaldehyde are increased when one considers that the formaldehyde is injected directly into the bloodstream and that these patients do not have kidneys which are able to detoxify these substances. In conclusion, I think the facts are inescapable that dialyzer reuse is not safe and efficacious. It is not safe both because of acute effects and because of the long-term risks of cancer. It is not efficacious because it has been well documented that with reuse, the efficiency of the dialyzer goes down. A question of concern is whether dialysis patients who reuse dialyzers should be allowed to choose between reuse and non-reuse and should not reuse dialyzers unless he has been given informed consent since there are risks involved. I also believe that because there are risks involved, patients should have the option to say no to their physician concerning reuse.

Should there be uniform Federal standards? The answer is yes: but what these Federal standards are is not at present certain. We need to know what the safest ways to sterilize dialyzers are, and that most certainly it is a subject that could be easily studied. We also need to know the optimal number of times that a dialyzer can be reused before it starts to lose efficiency. That also is a question that could be studied scientifically.

I would like to mention that in the United States in 1980 the cost for dialysis was $1.4 billion (Dialysis and Transplantation, Vol. 9, p. 23, 1980) (per telephone). In 1982 the cost of dialyzers was approximately $150 million (Artificial Organs, Vol. 6, p. 208, 1982). These figures allow one to calculate that the total cost of dialyzers is a relatively small portion of the total dialysis cost. Indeed, the number one costs are the costs that go to the hospitals and to the doctors. I really have always questioned whether the burden of trying to save money should come from the patients, when their contribution to the total cost is relatively small.

What are the best solutions to address these problems? The best solution would be to develop a safe way to reuse dialyzers. This is currently being worked on by a number of groups. A second solution is that a Federal study must be performed to determine guidelines for the optimal number of times that a dialyzer may be reused. Third, the installation of informed consent with freedom of choice would ensure that physicians would think twice before using a procedure that has potential side effects.

Chairman HEINZ. I must say, we have had some very insightful analyses of the studies that you all have mentioned.

Dr. Wolf, I think you mentioned one related issue here which has been cited as a reason to reuse dialyzers, and that is first-use syndrome. Let me ask you, to what extent is this phenomenon of first-use syndrome common or rare in your experience?

Dr. WOLF. In my experience, it is very rare. I think if you take a review of the literature it is probably fair to say maybe 3 percent, 5 percent of patients might experience this to a greater or lesser extent.

I don't see it that often and I think the reason for that is that we have gotten more and more biocompatible membranes as time goes on. I think some of the studies that showed first-use syndrome previously were with other membranes that have now been discontinued.

Dr. Oberley, what is your experience with this phenomenon?

Dr. OBERLEY. Well, personally I have no problem with first-use dialysis and in our dialysis units in Madison it is a very rare thing.

Chairman HEINZ. Do any of you believe that first-use syndrome, as some have argued, justifies reusing disposable dialyzers, blood lines and their transducer filters? It is used as a justification by some people.

Dr. WOLF. I don't think anything would justify the reuse of the blood lines and the transducers. First-use syndrome is a problem of the filter itself.

I think if you have someone who does have a severe first-use reaction and that person chooses to reuse because he feels better on reuse, I think that is part of the informed consent. That would be fine with me.

Chairman HEINZ. Dr. Oberley.

Dr. OBERLEY. I would have to agree. There are reports in the literature of patients with severe reactions to first-use of dialysis. They obviously should reuse; but, again, those are very rare occurrences.

Chairman HEINZ. Dr. Beall, in your testimony you referred to the NIH report of June 1981. Is that the Dean report that Dr. Wolf referred to, or is that the National Nephrology Foundation Report? Which report is that?

Dr. BEALL. I assume that it is the one to which Dr. Wolf referred.

Dr. WOLF. It is one and the same. The Dean report is the National Nephrology Foundation Report.

Chairman HEINZ. You, Dr. Beall, referred to an NIH report in June 1981.

Dr. BEALL. NIH, in June of 1981, had a report from the National Nephrology Foundation that was done under contract. So it is essentially the same report.

Chairman HEINZ. I think the answer is that we are really talking about the same report. The report was funded by NIH and written by the NNF, as I understand it. That report stated:

> The utilization of the specified procedures with suitable process and quality control would result in a reprocessed hollow-fiber hemodialyzer equivalent, in terms of functions, cleanliness and sterility, to a new hollow-fiber hemodialyzer.

Is this conclusion an accurate representation of the findings of that study?

Dr. **Beall**. The report is based on information from the subcontractor Authur D. Little, Inc. [ADL] that specifically states that there is a need for clinical validation of the work that was done. It was a combination of chemical analyses and in vitro studies. It had never been applied in a prospective clinical study and the ADL report, itself, indicated that it should be before being——

Chairman **Heinz**. So that is a misleading conclusion; what I stated was a misleading conclusion because there were no clinical studies.

Dr. **Beall**. That is correct.

Chairman **Heinz**. Now, there is a recent report entitled "Repeated Use of Dialyzers is Safe: Long-Term Observations on Morbidity and Mortality in Patients With End-Stage Renal Disease" which I understand is a private study. That report will be cited in testimony later this morning as showing that there are no problems with reusing disposable dialyzers.

Would you give us a brief assessment, if you have it, of that paper?

Dr. **Beall**. If you will let me get the paper out of my attaché, it would be helpful.

Chairman **Heinz**. Yes; by all means.

By the way, while Dr. Beall is getting that paper, I want to recognize the presence of Senator Hawkins of Florida who is a very active and concerned member of this committee. Earlier Senator Grassley was here. How he managed to get here I don't know because he was testifying before the Senate Banking Committee when I was up there between 9:30 and 10.

So we have some very versatile members here and some very interested ones, as well.

Dr. Beall.

Dr. **Beall**. That particular report that I believe you are referring to is the "Repeated Use of Dialyzers Is Safe" report that came out this year?

Chairman **Heinz**. That is right.

Dr. **Beall**. There are several problems with this report that need addressing before one should logically base on it their conclusions that reuse is safe. For example there were no controls in this particular report. It is a reporting of incidences that have occurred in two different units; there are no statistical analyses of the incidences. There is no comparison of incidences to those occurring with new use. All the dialyzers were reused. There are no analyses over time——

Chairman **Heinz**. So, first, there is no controlled sample.

Dr. **Beall**. That is correct. What they are doing is reporting incidences that have occurred in two different dialysis units or situations.

Chairman **Heinz**. So apart from the fact that they don't compare new first-time use versus reuse, which is a serious problem, are there any other problems in addition to that?

Dr. **Beall**. Well, there are indications that dialyzer function decreases with multiple reuse and there is no comparison over time of reuse. The type of analysis that needs to be done——

Chairman HEINZ. So what you are saying is they have not analyzed the extent to which multiple use impairs, or not, the ability of the filters to function effectively and the consequence effects on the patient.

Dr. BEALL. That is correct.

Chairman HEINZ. For example, reuses 1 through 10 may bring outcome x, reuses 40 through 50 may bring outcome z, and that was not studied.

Dr. BEALL. That is correct. Also there were no statistical analyses of the data that they did have so that the level of probability of change was never reported. And there was no real presentation of clinical data, clinical information.

It is more of a mortality/morbidity study of reactions; and, indeed, if you look at the data you can see that there is a numerical difference between the two dialysis centers. One wonders why two centers reusing dialyzers come out with apparently different results.

Chairman HEINZ. Since there are some 1,200 or 1,300 centers, if I remember correctly, would you consider two would be a sufficiently broad random sample? As I recollect from statistics, there is a complicated formula I never did quite master involving confidence levels.

My gut feel would be that a study of this kind using data from 2 of some 1,300 centers would have a confidence level well below 30 percent.

Dr. BEALL. You can place whatever percent you would like on the confidence. Mine is very low. I cannot quantitate it, though.

Chairman HEINZ. Maybe below 10 percent. [Laughter.]

Dr. BEALL. Clearly, the two centers were using a procedure that they felt confidence in and they report their incidence of occurrences, but there is really no study here.

Chairman HEINZ. I think that sums it up.

Dr. Wolf, you are really in an extraordinary position. You own a dialysis clinic. It is a for-profit clinic. You do not reuse. You actually follow the labels or, as you point out more importantly, you follow ethical practice.

Are you going broke?

Dr. WOLF. No. We are not making a whole lot of money either. I think if they were to take that last $10 away from me, I would.

To give you an example, we are a very small place. We have 10 stations, 60 patients running three shifts a day. That is small by most standards. There are places that have 20 or 30 chairs.

Even with our size unit, we do 10,000 treatments a year. That is $100,000 you are talking about, that's $10 a treatment.

Chairman HEINZ. As they say, that is real money.

Dr. WOLF. That is real money. That is $100,000 that I don't have that somebody else might have.

By the way, to go back, I think it is unfair to say that you save all the money on reuse. There is a fair cost associated with reusing a kidney.

Chairman HEINZ. How should we put numbers on that? What are the economics of reuse?

Dr. WOLF. First of all, I can buy a pretty good kidney for $10 or $11, a real good kidney. It is not a hollow-fiber dialyzer, it is a flat plate. It is not the kind you can reuse, but I don't have to buy that kind because I don't have to reuse.

You might spend $3 or $4 more for a hollow-fiber kidney. If you use that 10 times, which I think most people who ethically reuse, if you will allow me to use that assumption—I would say that 10 reuses is about the best you can do, any more than 10 and you are seriously impairing the efficiency of the dialyzer: that is the short-term efficacy—I think it probably cost somebody about $5 a reuse.

So you are cutting the cost by two-thirds. If you are paying, say, $14 or $15 for the equipment, it cost you about $5 each use to reuse it 10 times.

Chairman HEINZ. Now, Medicare reimburses you the same fee as somebody who reuses.

Dr. WOLF. Exactly.

Chairman HEINZ. Is there anything stated or implied in that reimbursement that one should or should not reuse these medical devices?

Dr. WOLF. No. As a matter of fact, every statement that I have ever seen on the topic of reuse starts out with an apologia, the first sentence, "We do not encourage or discourage reuse," and then they go on and say what they have to say.

Chairman HEINZ. One last question. In your statement, you note that:

> If Medicare and other third-party payers can rightfully withhold reimbursement for procedures such as plasmapheresis until they are of proven efficacy, it is reasonable to expect that the question of dialyzer reuse can be scrutinized.

Let's assume that is something of an understatement. Would it be appropriate for Medicare to withhold reimbursement of the reuse of this kind of medical equipment until standards are established, or is that too severe?

Dr. WOLF. I honestly think that would be too severe inasmuch as you have half the country reusing right now. They could stop reusing tomorrow, I think; but I think that, again to be fair to the people who reuse, there are people who reuse and believe in it.

As I stated before, I have no absolute data that says that reuse is bad. I am just not sure and I think that would be unjustified.

Chairman HEINZ. I think that is the consensus: Nobody has any studies that prove anything one way or the other.

Dr. WOLF. Nobody knows.

Chairman HEINZ. The reason I asked the question is that—and one always hopes to be surprised by future events—it has been some 8 years since the FDA's good manufacturing practices were first enacted into law. To say it is going slowly in this area is to say that water runs downhill.

How do we force the attention of the Federal agencies involved to do something unless we have a forcing device. I would like to think that as a result of your informed testimony and the examples of our earlier witnesses the Federal bureaucracy will get itself off its posterior and in gear. This does not always happen.

Should we say, well, 2 years from now unless standards are promulgated the Health Care Financing Administration will have to pick a time—2, 3, 4 years, 12 months; the Health Care Financing

Administration will have to withhold reimbursement until the studies are completed? Should we do something like that?

Dr. **Wolf**. Well, my own view is that it would take at least 5 years to show something. The reason I am saying that is I think that, again, the people who practice reuse well have shown to my satisfaction that, in the short term, you can reprocess a dialyzer and make it work as well as a new one; and you can do that, in optimum circumstances let's say, up to 10 times.

So I don't need anybody to prove that to me. I think I understand that.

What I don't understand is what is going to happen to a matched population of used dialyzers and new dialyzers over the long term, and the long term is 5 years, I think, at the shortest.

Chairman **Heinz**. Well, here is my question. I address it to all of you.

We all agree studies are needed; we all agree standard procedures and so forth are necessary. It may take a long time to get the clinical results we need.

Should we just sit back and wait and let current practice take its course for the next 5 years, or is there something that should happen in the meantime, such as interim guidelines?

Dr. Beall, do you want to tackle that one?

Dr. **Beall**. Well, I have few thoughts on it. I feel a little ambivalent since I am part of the bureaucracy that we are talking about, except that I work for a different agency that has no interest——

Chairman **Heinz**. So do we. [Laughter.]

Dr. **Beall**. That is true.

I think clearly there are steps that can be taken prior to waiting for data to come in. I think in terms of lead poisoning, which the Romans knew about and of which we are still studying the mechanism, I don't think we could wait forever on this particular issue. I think the dialysis patients certainly have a right to informed consent and choice. I don't think we need to wait too much longer for that even if the best we can inform them is we are not certain what the outcome might be under the two choices.

I think that steps can be taken to eliminate the coercion that occurs in some dialysis treatment centers. Studies can be initiated and interim reports of them may be useful.

I know that a literature review and a number of fundamental or foundation types of work have already been done. So in a sense we can pick up in the middle on some of these things and carry on with them.

So I would suggest that some actions be taken relatively soon and studies be initiated, and appropriate follow up occur in a timely fashion so that we can see the progress of these studies and capitalize on the information they produce as readily as possible.

Chairman **Heinz**. Dr. Oberley.

Dr. **Oberley**. I think the first rule of any physician is to do no harm, and I think we have breached that violation with many of the things we are doing in reuse.

I would like to point out, No. 1, that we could establish informed consent immediately; and, No. 2, I think we could stop what I consider the worst thing: the continued reuse of dialyzers over a safe level. That would not take 5 years to find out.

We could find out what a safe level is to reuse dialyzers in the next 6 months. I submit that it is unacceptable to reuse dialyzers 30 times. I don't care who it is and how good they are reusing dialyzers, the creatinine, the waste products, are going to go up after that much reuse and the patient is going to be at risk.

So I think we can establish, in 6 months, what is the safe number of times to reuse dialyzers, and then we could institute that as a law. I submit that would be the best thing we could do for the patients right now.

Chairman **Heinz**. Do any of you disagree with that last recommendation?

Dr. **Wolf**. I submit that we already know that. I think that we have already reasonable data saying what short-term procedures should be used.

I also submit that all of the people who I know—who, again if you will forgive me, practice ethical reuse—have no trouble meeting those standards right today. So I don't think you will be hurting anybody who is doing a good job by establishing standards.

In fact, you will be helping them because then you don't have the guy down the street doing a worse job and the rest of us getting the blame for it.

Dr. **Oberley**. But I would like to submit that I have here the record of a patient who routinely reused dialyzers 21 times in 1984. What do we do about that?

Dr. **Wolf**. I agree. I think that we need to establish standards. I think that most of the data around, just as a rough number, shows that after 10 reuses the efficacy of the filter falls by 10 percent, 20 percent at the most. That is it.

Now, you can find an occasional kidney that can go out 20 times, but why should you?

Chairman **Heinz**. Senator Hawkins, I yield to you for any opening statement or questions, or both.

STATEMENT BY SENATOR PAULA HAWKINS

Senator **Hawkins**. I have been conducting a subcommittee hearing myself which both Senator Grassley and Senator Dodd attended.

Why would you wait 5 years? I am so tired of studies. We are just weighed down with studies. I mean, that is the oldest business in this city and you are talking about lives, you are talking about safety.

We will just say that if you use the dialysers more than 5 times or 6 times, the economies of scale they will not cost you as much, therefore we just will not reimburse you as much. If you are a clinic that does it 50 times, you just don't get as much money as if you are one that does it like yours, just a single time.

We can implement the reimbursement schedule immediately. I am also concerned about the issue of informed consent. What are you going to tell the patient? This may or may not be safe, therefore, we want you to sign off on liability.

How long until you have some statistics? What are you going to say to the patient? I mean, informed consent, everybody is using that word so wonderfully here—informed consent. I don't know what it is going to say on the informed consent form.

What you are doing is talking about liability. I think there is a lot of liability to go around here, just walking in and seeing what is going on and the total number of these clinics across the United States. There are two things I am concerned about.

I don't think we could even word what an informed consent form could say today that would put all the liability on the patient's side, which is where we like to shove it.

No. 2, I don't know whether the patient has freedom of choice to go to another clinic. When you are saying that the patient can go to a clinic that uses it once or they can choose one that does it 10 times or 30 times, you are assuming both clinics are easily accessable. I don't think they have that freedom of choice yet.

When you deal with the reality of it today, what are you going to do tomorrow? It is great to have hearings. We have them all over this building in all this Capitol. You could go to a hearing any time you want to.

But the results should be, after the hearing, we act on this problem. I would rather err on the side of caution while we are doing the 5-year study. I don't want to wait until the 5-year study is completed to act.

I think that bureaucrats like to do 5-year studies. I don't think we should. I think we have evidence, from just the little bit I have read here and letters we have gotten in Florida where we have probably our fair share of people that have had this problem, that we should look at the reimbursement schedules, Mr. Chairman, of those clinics that use it more than one time; and I think you have to get more than Philadelphia lawyers who could write an informed consent that would be real informed consent to this practice.

Chairman **Heinz**. Now, easy there, Senator Hawkins. [Laughter.] That is a very large number of Philadelphians.

Senator **Hawkins**. I spoke to them once.

Chairman **Heinz**. While I might, in secret, share some of your reservations about lawyers, please don't single out Philadelphia lawyers.

Senator **Hawkins**. I spoke to the Philadelphia lawyers once and I was intrigued: they had to meet in Atlantic City. [Laughter.]

Chairman **Heinz**. Our next panel of witnesses will be representatives of the administration, with a number of administrative and bureaucratic responsibilities concerning these issues.

As he says, Dr. Beall is a little nervous about being here. He wears two hats: one as a public servant and one as an informed citizen, which is the main hat he is wearing here today.

I hope you are still wearing two when you get back.

Dr. **Beall**. Oh, I will be. I work in the Department of Energy and that agency has little interest in dialyzers, as far as I am aware.

Chairman **Heinz**. Then you are all right, I think.

By the way, I am intruding on Senator Hawkins——

Senator **Hawkins**. It is on my time.

Chairman **Heinz** [continuing]. And I apologize.

Senator **Hawkins**. It is all right. He does all the time. Go ahead. [Laughter.]

Dr. Beall. All I wanted to indicate is that I had investigated this as an academic subject of interest to me as a toxicologist. That is the information I have provided.

Senator Hawkins. We appreciate it.

Chairman Heinz. Any other questions, Senator?

Senator Hawkins. No.

Chairman Heinz. I would like to thank our three witnesses for some extraordinarily informed testimony. I think you have given us some very specific concrete suggestions as to freedom of choice, informed consent, specific standards that can now be set as well as studies that can and should be done now to fine tune over the long term the ultimate decisions on the question of reuse standards for reprocessing and reuse of these devices.

These are all issues that do, as you have all indicated, need to be addressed; but they are not an excuse for not taking some very important steps right now.

We thank you all very much.

Our last panel of witnesses represents the administration. Dr. John E. Marshall is the Director of the National Center for Health Services Research and Health Care Technology Assessment; Mr. Bart Fleming is the Acting Deputy Administrator of the Health Care Financing Administration, which has been mentioned numerous times here today.

Gentlemen, we welcome you. Dr. Marshall, it is my understanding that, in a sense, you are here representing both your center as well as the Food and Drug Administration. You are really the witness designated by the Public Health Service, of which you are a distinguished part, to testify on behalf of the Public Health Service. So let me ask you to please proceed.

STATEMENT OF JOHN E. MARSHALL, PH.D., DIRECTOR, NATIONAL CENTER FOR HEALTH SERVICES' RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT, PUBLIC HEALTH SERVICE, ACCOMPANIED BY DR. JOHN VILLFORTH, DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION

Dr. Marshall. That is correct, Senator. Thank you. I appreciate it.

I am accompanied by Dr. John Villforth who is the Director for the Center for Devices and Radiological Health of the Food and Drug Administration. So to the extent that we get into questions where some of the details or some of the observations might more appropriately come from him, I will ask him to make responses.

He and I are both here as representatives of the Assistant Secretary for Health's Office for the Public Health Service. I have a statement which we have submitted for the record.

Chairman Heinz. Without objection, your entire statement will be a part of the record.

[The prepared statement of Dr. Marshall follows:]

PREPARED STATEMENT OF JOHN E. MARSHALL, PH.D.

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE, I AM JOHN E. MARSHALL, PH.D., DIRECTOR OF THE NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT. THE NATIONAL CENTER PROVIDES THE FOCAL POINT WITHIN THE PUBLIC HEALTH SERVICE (PHS) FOR SYNTHESIZING SCIENTIFIC AND CLINICAL INFORMATION FROM THE NATIONAL INSTITUTES OF HEALTH (NIH), FOOD AND DRUG ADMINISTRATION (FDA), CENTERS FOR DISEASE CONTROL (CDC), AND OTHER PHS ELEMENTS FOR USE BY THE HEALTH CARE FINANCING ADMINISTRATION (HCFA) IN DETERMINING MEDICARE POLICY. WITH ME TODAY IS DR. JOHN C. VILLFORTH, DIRECTOR OF THE CENTER FOR DEVICES AND RADIOLOGIC HEALTH, WHICH IS THE OPERATIONAL ARM OF THE FDA CHARGED WITH REGULATING MEDICAL DEVICES. WE ARE TODAY REPRESENTING THE ASSISTANT SECRETARY FOR HEALTH AND TO DISCUSS PUBLIC HEALTH SERVICE ACTIVITIES REGARDING THE REPROCESSING AND REUSE OF DISPOSABLE HEMODIALYSIS DEVICES. MR. CHAIRMAN, I WOULD LIKE TO ASSURE THIS COMMITTEE THAT WE SHARE A MUTUAL CONCERN FOR THE SAFETY AND WELL BEING OF AMERICANS UNDERGOING CHRONIC MAINTENANCE HEMODIALYSIS. THE PUBLIC HEALTH SERVICE HAS BEEN INVOLVED IN PROVIDING THE SCIENTIFIC AND CLINICAL SUPPORT FOR THE END-STAGE RENAL DISEASE PROGRAM FROM THE VERY BEGINNING AND WE ARE PREPARED TO ASSESS AND ACT PROMPTLY ON ANY SCIENTIFIC DATA WHICH SUGGESTS THE NEED FOR CHANGE IN CURRENT POLICIES.

BACKGROUND

THE REUSE OF DISPOSABLE HEMODIALYSIS DEVICES WAS FIRST PROPOSED BY SHALDON IN 1963 AND REPORTED BY SCRIBNER IN 1967. SHALDON

PERFORMED DAILY DIALYSIS IN BRITAIN BUT WAS ONLY ALLOWED 3 FILTERS A WEEK BY THE HOSPITAL. THIS NECESSITATED REUSE OF THE DIALYZER. AT THAT TIME HE NOTED THAT IT WAS FEASIBLE, SAFE, AND ASSOCIATED WITH FEWER COMPLICATIONS THAN WAS THE FIRST USE OF A NEW DIALYZER. DAVID OGDEN LATER REPORTED THE "PHENOMENON OF REACTION TO NEW DIALYZERS," WHICH HE ASSOCIATED WITH THE DEVELOPMENT OF RESPIRATORY DISTRESS, WHEEZING, MALAISE, BACK OR CHEST PAIN, FEVER AND CHILLS AT THE BEGINNING OF TREATMENT. WITH RECENT IMPROVEMENTS IN DIALYZER TECHNOLOGY, THIS SYNDROME IS MUCH MILDER AND ASSOCIATED WITH WEAKNESS, DIZZINESS AND MALAISE. ASIDE FROM VIRTUALLY ELIMINATING THE EFFECTS OF FIRST USE SYNDROME, REUSE HAS BEEN ASSOCIATED WITH LOWER COST.

FOLLOWING THE PASSAGE OF THE SOCIAL SECURITY AMENDMENTS OF 1972 WHICH EXTENDED MEDICARE COVERAGE TO PATIENTS WITH END-STAGE RENAL DISEASE, REUSE DROPPED OFF SLIGHTLY, BUT BY 1981 THIS FIGURE HAD RISEN TO OVER 27 PERCENT. IN THE MEANTIME, SUBSTANTIAL EXPERIENCE WITH REUSE WAS REPORTED FROM 5 COUNTRIES IN EUROPE. THAT EVIDENCE REVEALED NO DIFFERENCE IN SURVIVAL BETWEEN PATIENTS FOR CENTERS WHERE HEMODIALYSIS DEVICES WERE REUSED. IN FACT THERE WAS A SLIGHT TREND TOWARDS A LOWER MORTALITY WITH REUSE AS OPPOSED TO SINGLE USE. A RECENT STUDY (POLLAK, ET AL, 1986) INVOLVING 1300 PATIENTS OVER SEVEN YEARS SHOWED NO DIFFERENCE IN MORBIDITY, MORTALITY OR DAYS OF HOSPITALIZATION BETWEEN SINGLE AND MULTIUSE PATIENTS.

WHILE REUSE OF HEMODIALYZERS HAS BECOME STANDARD MEDICAL PRACTICE

IN OVER 60 PERCENT OF DIALYSIS CENTERS, ACCORDING TO 1983 STATISTICS, ANNUAL MORTALITY AMONG PATIENTS ON HEMODIALYSIS REMAINS CONSTANT DESPITE THIS INCREASING TREND. THIS RATE OF MORTALITY HAS NOT CHANGED OVER THE LAST SEVERAL YEARS.

REUSE SAFETY

THE PUBLIC HEALTH SERVICE VIEWS REUSE OF HEMODIALYZERS AS A CLINICAL JUDGMENT DECISION ON THE PART OF THE PHYSICIAN, AND BECAUSE WE SEE NO HEALTH HAZARDS ASSOCIATED WITH THIS PRACTICE IF DONE PROPERLY, WE NEITHER ADVOCATE NOR RECOMMEND AGAINST REUSE. OUR POSITION IS BASED ON A NUMBER OF STUDIES ON THE SAFETY OF DIALYZER REUSE. IN RESPONSE TO CONGRESSIONAL INTEREST, THE NATIONAL INSTITUTES OF HEALTH IN 1979 EMBARKED ON A PILOT STUDY TO "OBTAIN INFORMATION ON PROCEDURES FOR MULTIPLE USE OF HEMODIALYZERS" PARTICULARLY WITH RESPECT TO STERILIZATION AND FUNCTIONING. THAT STUDY, ENTITLED, "MULTIPLE USES OF HEMODIALYZERS" CONCLUDED THAT "...THE CARE WITH WHICH A REPROCESSING PROCEDURE WAS APPLIED WAS CRITICAL FOR SATISFACTORY CLINICAL RESULTS. WHERE ATTENTION TO DETAIL SLACKENED OR THE METHOD WAS INADEQUATE, EVIDENCE OF COMPLICATIONS OF THE TECHNIQUE WERE ENCOUNTERED." THE REPORT FURTHER STATED THAT "UTILIZATION OF THE SPECIFIED PROCEDURES WITH SUITABLE PROCESS AND QUALITY CONTROL WOULD RESULT IN A REPROCESSED HOLLOW FIBER HEMODIALYZER EQUIVALENT IN TERMS OF FUNCTION, CLEANLINESS, AND STERILITY TO A NEW HOLLOW FIBER HEMODIALYZER."

IN ADDITION TO THIS STUDY, FDA IN 1980 SPONSORED A STUDY TO investigate the risks and hazards associated with hemodialysis systems. That study also focused on dialyzer reuse and reprocessing and found that patients undergoing dialysis treatment with reused dialyzers were at no greater risk than patients being treated with new dialyzers if adequate reprocessing was performed. Finally, in 1981-1982, the National Center for Health Care Technology, whose functions NCHSR has now assumed, coordinated a public-private sector conference co-sponsored by the FDA. It resulted in the first consensus on guidelines for the reuse of disposable dialysis equipment, the forerunner to the guidelines now under development by the Association for the Advancement of Medical Instrumentation. The conference guidelines were designed to assist those who undertake this practice to enable them to do so in a manner that would protect dialysis patients.

In 1982, the Department convened an inter-Departmental end-stage renal disease strategic work group. This group evaluated a range of issues pertaining to end-stage renal disease. Where their report pertained to reuse, this group recommended that clinical trials be performed to assess the process, the safety and efficacy of this practice. A second work group designated the Public Health Service ESRD Coordinating Committee was subsequently formed by the Assistant Secretary for Health. This Committee reported back in 1983 suggesting that clinical trials were unnecessary, but instead a data base should be developed jointly by the Health Care Financing Administration and the

PUBLIC HEALTH SERVICE IN ORDER TO OBTAIN INFORMATION ON A WIDE RANGE OF ESRD-RELATED ISSUES INCLUDING REUSE. LAST SEPTEMBER, NIH ENTERED INTO AN INTERAGENCY AGREEMENT WITH HCFA TO DEVELOP SUCH A JOINT DATA BASE AIMED AT ANSWERING QUESTIONS IN A NUMBER OF CATEGORIES, ONE OF WHICH RELATES TO THE REUSE OF HEMODIALYSIS DEVICES.

IN TERMS OF REGULATORY POLICY, WHICH I KNOW MR. CHAIRMAN FROM YOUR LETTER TO FDA COMMISSIONER YOUNG IS OF PARTICULAR INTEREST TO YOU, LET ME POINT OUT THAT TRADITIONALLY, FDA'S POLICY HAS BEEN THAT THE DECISION TO REUSE A DIALYZER IS UP TO THE PHYSICIAN. THIS POLICY WAS OUTLINED IN A GUIDE PUBLISHED IN 1977 AND REVISED IN 1981. IT PLACES THE RESPONSIBILITY FOR REUSE ON THE USER. IT STATES THAT THE INSTITUTION OR PRACTITIONER REUSING ANY DISPOSABLE DEVICE SHOULD BE ABLE TO DEMONSTRATE THAT: (1) THE DEVICE CAN BE ADEQUATELY CLEANED AND STERILIZED; (2) THE PHYSICAL CHARACTERISTICS OR QUALITY OF THE DEVICE WILL NOT BE ADVERSELY AFFECTED; AND (3) THE DEVICE REMAINS SAFE AND EFFECTIVE FOR ITS INTENDED USE. THE POLICY ALSO STATES THAT THE INSTITUTION OR PRACTITIONER WHO STERILIZES OR REUSES A DEVICE LABELED AS DISPOSABLE MUST BEAR FULL RESPONSIBILITY FOR ITS SAFETY AND EFFECTIVENESS.

AT THE TIME THESE POLICIES WERE ENUNCIATED, THE REUSE OF HEMODIALYZERS WAS RELATIVELY INFREQUENT, ON THE ORDER OF 16 PERCENT ACCORDING TO THE 1980 REPORT PREPARED FOR FDA. AT THAT TIME, THOSE FACILITIES WHICH REUSED DIALYZERS GENERALLY HAD

SUFFICIENT EXPERIENCE AND EXPERTISE IN THIS PROCEDURE SO THAT PROBLEMS WERE THOUGHT TO BE MINIMAL. CURRENTLY APPROXIMATELY 60 PERCENT OF DIALYZED PATIENTS ARE TREATED WITH REUSED DIALYZERS. THIS INCREASES THE POTENTIAL FOR PROBLEMS RELATED TO INADEQUATE REPROCESSING TECHNIQUES FOR TWO REASONS: THE SHEER INCREASE IN THE NUMBER OF REPROCESSING PROCEDURES BEING CONDUCTED, AND AN INCREASE IN THE NUMBER OF FACILITIES PERFORMING THESE PROCEDURES, SOME OF WHICH MAY HAVE LITTLE EXPERIENCE IN REPROCESSING.

BECAUSE OF THE INCREASING TREND IN REUSE, FDA IS ALSO DEVELOPING A COMPREHENSIVE POLICY ON REUSE FOR MEDICAL DEVICES ACROSS-THE-BOARD. I SHOULD EMPHASIZE THAT THIS POLICY STATEMENT IS IN ITS EARLY FORMATIVE STAGES. FDA IS EXAMINING A VARIETY OF OPTIONS, INCLUDING WHETHER TO IMPOSE ADDITIONAL LABELING REQUIREMENTS ON MANUFACTURERS, AND WHETHER ITS EXISTING AUTHORITY APPLIES TO THOSE WHO REPROCESS MEDICAL DEVICES SUCH AS DIALYZERS.

LET ME ADD THAT THERE ARE SEVERAL OTHER FACTORS THAT MAY AFFECT PATIENT OUTCOME. FOR EXAMPLE, THE PURITY OF WATER USED IN DIALYSIS TREATMENTS MAY HAVE A FAR GREATER IMPACT THAN ANY CONSIDERATIONS OF REUSE. IN ADDITION, HUMAN ERROR SUCH AS THE USE OF IMPROPER DIALYSATE MIXTURE AND IMPROPER FLUID TEMPERATURES CAN HAVE FATAL EFFECTS. FDA IS TAKING ACTION TO ASSESS POTENTIAL PROBLEMS IN THE FIELD OF DIALYSIS AND TO MAKE THE PROCESS AS SAFE AS POSSIBLE. FOR EXAMPLE, FDA HAS COLLABORATED WITH AAMI IN THE DEVELOPMENT OF A VOLUNTARY PERFORMANCE STANDARD ON HEMODIALYSIS SYSTEMS, WHICH WAS PUBLISHED IN 1981, AND WHICH INCLUDES

REQUIREMENTS FOR, AMONG OTHER PARAMETERS, WATER QUALITY. ADDITIONALLY, THE FDA HAS CONTRACTED WITH THE HEALTH DEPARTMENTS OF THREE STATES AND THE DISTRICT OF COLUMBIA TO INVESTIGATE THE NATURE AND FREQUENCY OF PROBLEMS THAT CAN BE LINKED TO USER ERROR. THE FINDINGS OF THIS INVESTIGATION WILL HELP IN THE DEVELOPMENT OF SPECIFIC EDUCATIONAL PROGRAMS FOR DIALYSIS FACILITIES.

THE CENTERS FOR DISEASE CONTROL HAS ALSO BEEN INVOLVED IN EVALUATING EVENTS SURROUNDING THE REUSE OF HEMODIALYZERS. IN 1982, AN OUTBREAK OF NONTUBERCULAR MYCOBACTERIAL INFECTIONS WAS REPORTED IN LOUISIANA AT A DIALYSIS CENTER ENGAGED IN REUSE OF DISPOSABLE DIALYZERS. OF THE 140 PATIENTS TREATED AT THE FACILITY, 27 PATIENTS DEVELOPED INFECTIONS, SOME SEVERE. OF THESE, 14 PATIENTS DIED. WATER CONTAMINATION BY MYCOBACTERIA WAS FOUND TO BE THE CAUSE OF THIS OUTBREAK AT THAT FACILITY. CDC THEN PERFORMED STUDIES AIMED AT UNDERSTANDING WHAT LEVELS OF GERMICIDE WERE REQUIRED IN THE RINSING WATER TO PREVENT INFECTING DIALYZER FILTERS THROUGH WHICH HUMAN BLOOD WAS TO BE EXPOSED. IT WAS NOTED THAT WITH FORMALDEHYDE AT 2 PERCENT, SOME BUT NOT ALL BACTERIA WERE ELIMINATED. AT CONCENTRATIONS OF 4 PERCENT ALL INFECTING ORGANISMS WERE ELIMINATED. IN 1983, SCIENTISTS FROM THE CENTERS FOR DISEASE CONTROL WHO PARTICIPATED IN AN AAMI TECHNOLOGY ASSESSMENT CONFERENCE ON REUSE OF DISPOSABLES INDICATED THAT "BY APPLYING GOOD TECHNIQUES, ADHERING TO RIGID PROTOCOLS, AND BY USING HIGH-LEVEL DISINFECTANT PROCEDURES, WHICH NOW MEANS 4 PERCENT FORMALDEHYDE, IT SEEMS THAT DIALYZERS CAN BE

REUSED WITHOUT UNDUE RISK OF INFECTIONS OR PYROGENIC REACTIONS TO DIALYZING PATIENTS."

IN 1984 A FOLLOW UP NATIONWIDE SURVEY WAS PERFORMED BY CDC IN CONNECTION WITH THE HCFA FACILITIES SURVEY. A RANDOM SAMPLING OF 115 CENTERS WAS CONDUCTED UNDER FUNDING BY THE HEALTH CARE FINANCING ADMINISTRATION. AFTER INSPECTING WATER SAMPLES, 70 PERCENT OF LOCAL CITY WATER, AND 48 PERCENT OF RESPECTIVE DIALYSIS CENTER WATER USED FOR DIALYSIS SAMPLES WERE FOUND TO CONTAIN MYCOBACTERIA. DURING THIS SURVEY ONLY 3 PATIENTS FROM THE 115 CENTERS WERE FOUND TO BE INFECTED WITH THE CONTAMINATING ORGANISM. THIS WAS NOT A SIGNIFICANT RATE OF INFECTION. ANOTHER SURVEY WAS CONDUCTED BY CDC IN CONNECTION WITH HEPATITIS B AIMED AT DETERMINING WHETHER THE INCIDENCE OF HEPATITIS B IN PATIENTS AND STAFF WAS GREATER IN CENTERS THAT PRACTICED REUSE. NO GREATER INCIDENCE WAS FOUND IN THOSE CENTERS WHERE REUSE WAS PRACTICED AS COMPARED TO THOSE WHERE IT WAS NOT. THE CDC CONTINUES TO PERFORM AN ANNUAL FACILITY SURVEY IN CONNECTION WITH THE SURVEY PERFORMED BY THE HEALTH CARE FINANCING ADMINISTRATION TO DETERMINE WHETHER THE RATE OF DIALYSIS CENTER INFECTION INCREASES WITH REUSE OR IS GREATER IN CENTERS THAT REUSE AS COMPARED WITH THOSE THAT DO NOT. TO DATE NO DIFFERENCE HAS BEEN DEMONSTRATED.

THE NATIONAL INSTITUTES OF HEALTH CONDUCTS RESEARCH ACTIVITIES RELATIVE TO ESRD. IN OCTOBER 1985, THE NATIONAL INSTITUTE OF APTHRITIS, DIABETES, DIGESTIVE AND KIDNEY DISEASES AND THE HEALTH

CARE FINANCING ADMINISTRATION FINALIZED AN INTERAGENCY AGREEMENT TO COLLABORATE IN A NATIONAL END-STAGE RENAL DISEASE PATIENTS REGISTRY. THIS AGREEMENT COVERS THE SHARING OF PATIENT-SPECIFIC DEMOGRAPHIC AND MEDICAL INFORMATION ON THE ESRD POPULATION FOR THE PURPOSES OF RESEARCH, AND FOR THE PRODUCTION OF PROFILES ON ESRD PATIENTS AND PROVIDERS AND OF RELATED ANALYSES.

UNDER THE TERMS OF THIS AGREEMENT, HCFA WILL BE RESPONSIBLE FOR DATA ACQUISITION, VALIDATION AND MANAGEMENT AND WILL MAKE AVAILABLE, ON AN ONGOING BASIS, DEMOGRAPHIC AND MEDICAL INFORMATION COVERING ESRD PATIENTS TO THE NIADDK CHRONIC RENAL DISEASE PROGRAM. NIADDK WILL PROVIDE BIOMEDICAL AND BIOSTATISTICAL EXPERTISE AS NECESSARY TO DEVELOP AND IMPLEMENT THE NATIONAL ESRD PATIENT REGISTRY.

APPROXIMATELY 15 TYPES OF RESEARCH QUESTIONS AND/OR DIRECTIONS WILL BE ADDRESSED. EXAMPLES INCLUDE: BIOCOMPATIBILITY, THAT IS RELATIONSHIP OF BLOOD PRODUCTS, MACHINERY, AND MATERIALS; DIALYSATES; DIALYSER REUSE; DETERMINANTS OF LONG-TERM SURVIVAL; ACUTE-PHASE REACTANTS; POST-DIALYSIS SYNDROME; AND VASCULAR ACCESS PROBLEMS.

THE PHS HOPES THAT THE ESTABLISHMENT OF A NATIONAL END-STAGE RENAL DISEASE PATIENTS REGISTRY WILL ALLOW THE IDENTIFICATION AND/OR FURTHER EVALUATION OF INDIVIDUAL AREAS IMPORTANT TO THE MANAGEMENT OF ESRD.

FORMALDEHYDE

MR. CHAIRMAN, FORMALDEHYDE WAS THE MOST COMMONLY USED DISINFECTANT FOR REPROCESSING HEMODIALYZERS IN 1983. TWO PERCENT WAS THE MOST COMMON CONCENTRATION. CDC LABORATORY INVESTIGATIONS OF THE OUTBREAK OF MYCOBACTERIAL INFECTIONS ASSOCIATED WITH REPROCESSED HEMODIALYZERS FOUND THAT THE MYCOBACTERIA IMPLICATED IN THE OUTBREAK WERE HIGHLY RESISTANT TO FORMALDEHYDE DISINFECTANTS. IN LABORATORY TESTS, THESE ORGANISMS COULD SURVIVE A 96-HOUR EXPOSURE TO A 2 PERCENT FORMALDEHYDE SOLUTION. THESE FINDINGS INDICATED THAT STORING HEMODIALYZERS IN 2 PERCENT FORMALDEHYDE COULD NOT RELIABLY PRODUCE A MICROBIOLOGICALLY ACCEPTABLE HEMODIALYZER. OUR STUDIES HAVE INDICATED THAT HIGH CONCENTRATIONS OF GERMICIDE-RESISTANT MYCOBACTERIA ARE KILLED BY 24 HOURS OF EXPOSURE TO 4 PERCENT FORMALDEHYDE.

STUDIES HAVE SUGGESTED THAT FORMALDEHYDE PRODUCES TUMORS IN RATS WHEN INHALED. HOWEVER NO EVIDENCE EXISTS TO SUGGEST THAT VERY LOW DOSE EXPOSURE TO THIS SUBSTANCE IN THE BLOOD HAS CAUSED A SIMILAR EFFECT. I SHOULD EMPHASIZE THAT MR. CHAIRMAN, FORMALDEHYDE IS PRESENT AT PHYSIOLOGIC LEVELS IN HUMAN BLOOD AS A RESULT OF METABOLISM AND THE BREAKDOWN OF FAT AND OTHER SUBSTANCES. THIS SUBSTANCE IS RAPIDLY DEGRADED BY THE BODY. WHEN FORMALDEHYDE IS USED TO DISINFECT DIALYZERS, THE RINSING AND STORAGE PROCESS RESULT IN MINUTE RESIDUAL AMOUNTS OF FORMALDEHYDE IN FILTERS. PROCEDURES HAVE BEEN WORKED OUT THAT WOULD ENABLE

THOSE WHO REPROCESS DIALYZERS TO PROPERLY RINSE AND REMOVE RESIDUAL FORMALIN FROM THE DIALYZERS TO LEVELS CERTAINLY BELOW 5 PARTS PER MILLION. ADVERSE REACTIONS TO RESIDUAL FORMALDEHYDE HAVE BEEN INFREQUENTLY REPORTED.

THE PRESENCE OF ANTI-N-LIKE ANTIBODIES HAS BEEN OBSERVED IN PATIENTS IN WHOM THE EFFLUENT FROM THE DIALYZERS PREPARED FOR REUSE WAS GREATER THAN 10 PARTS PER MILLION. ANTI-N-LIKE ANTIBODIES RARELY DEVELOP BELOW THAT LEVEL AND WERE NEVER SEEN BELOW 3 PARTS PER MILLION. THESE ANTIBODIES HAVE BEEN ASSOCIATED WITH DEVELOPMENT OF ANEMIA, LOW BLOOD PRESSURE, AND GRAFT WASTING IN SOME RECIPIENTS OF RENAL TRANSPLANTS IF THE KIDNEY WAS NOT WARMED PRIOR TO IMPLANTATION. ANEMIA REQUIRING INCREASED REQUIREMENTS OF BLOOD TRANSFUSIONS HAS BEEN SUGGESTED TO BE A COMPLICATION OF ANTI-N-LIKE ANTIBODIES BUT I WANT TO EMPHASIZE THAT THESE ANTIBODIES HAVE NOT BEEN OBSERVED WHEN CONCENTRATIONS OF EFFLUENT FORMALDEHYDE ARE BELOW 3 PARTS PER MILLION.

OTHER REACTIONS TO RESIDUAL FORMALDEHYDE HAVE BEEN REPORTED. THESE RANGE FROM LOCALIZED BURNING, NUMBNESS OF THE LIPS AND TONGUE, BURNING EXTREMITIES, AND TIGHTNESS IN THE THROAT. ANALYSIS OF MOST REPORTS OF SUCH REACTIONS SUGGESTS THAT IN ALL CASES, THE FORMALDEHYDE INFUSED WAS SIGNIFICANTLY MORE THAN IS RECOMMENDED AT PRESENT. MONITORING OF FORMALDEHYDE IN THESE CENTERS INVOLVED THE USE OF "CLINITESTS, DIP STICKS" TO DETECT FORMALDEHYDE IN THE EFFLUENT SOLUTION. THIS METHOD OF TESTING IS RELATIVELY INSENSITIVE TO THE DETECTION OF FORMALDEHYDE. WHEN

ACCURATE DETERMINATION OF FORMALDEHYDE HAS BEEN PERFORMED WITH THE "SHIFF REAGENT" FOR WHICH SENSITIVITY IS 1000 TIMES GREATER THAN THE CLINITEST, NO REPORTS OF CLINICALLY ADVERSE EFFECTS OF FORMALDEHYDE HAVE BEEN REPORTED.

IN SUMMARY, MR. CHAIRMAN, APPROXIMATELY 78,000 PATIENTS ARE TREATED ANNUALLY BY CHRONIC MAINTENANCE HEMODIALYSIS AT 1400 DIALYSIS CENTERS NATIONWIDE AND AT A COST OF SOME $2 BILLION PER YEAR NOT INCLUDING HOSPITALIZATION. SOME 12 MILLION DIALYZERS ARE SOLD EACH YEAR OF WHICH 90 PERCENT ARE SUPPLIED BY 6 MANUFACTURERS. THE PRACTICE OF REUSING DIALYSIS DEVICES HAS INCREASED FROM 16 PERCENT IN 1978 TO OVER 60 PERCENT IN 1983. DESPITE DRAMATIC INCREASES IN THE RATE OF REUSE, NO CHANGE IN THE ANNUAL MORTALITY AMONG DIALYSIS PATIENTS HAS BEEN OBSERVED. WHILE THE PUBLIC HEALTH SERVICE NEITHER ENDORSES NOR CONDEMNS REUSE, IT HAS PARTICIPATED IN THE DEVELOPMENT OF VOLUNTARY GUIDELINES BEING PROPOSED BY THE ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. THESE GUIDELINES WILL ADDRESS THE REUSE, REPROCESSING AND DISINFECTION/STERILIZATION. THE INCIDENCE OF COMPLICATIONS ASSOCIATED WITH REUSE APPEARS LOW. INFECTION, WHETHER HEPATITIS B OR PYROGENIC, APPEARS TO BE NO GREATER AMONG RECIPIENTS OF REUSED DIALYZERS THAN AMONG THOSE ALWAYS DIALYZED WITH NEW DIALYZERS. OVERALL MORBIDITY AND MORTALITY IS NO DIFFERENT BETWEEN THE TWO GROUPS. THERE APPEARS TO BE A DIFFERENCE IN THE DEVELOPMENT OF ANTI-N-LIKE ANTIBODIES WHICH OCCUR IN LESS THAN 30 PERCENT OF PATIENTS ON REUSE. HOWEVER THESE ANTIBODIES APPEAR TO CORRELATE WITH FORMALDEHYDE

LEVELS EXCEEDING 10 PARTS PER MILLION AND HAVE NEVER BEEN ASSOCIATED WITH LEVELS BELOW 3 PARTS PER MILLION.

REPORTS OF PARTICULATE CONTAMINATION OR PYROGEN REACTION HAVE BEEN SEEN IN 22 INSTANCES OF REUSED DIALYZERS, THE INCIDENCE IS SIGNIFICANTLY HIGHER IN FIRST USE DIALYZERS AND APPEARS TO BE ASSOCIATED WITH THE LEECHING OF TOXINS AND/OR PYROGENS FROM CUPROPHANE AND CELLULOSE ACETATE FILTERS. TWENTY-TWO YEARS OF EXPERIENCE WITH DIALYZER REUSE IN LARGE NUMBERS OF PATIENTS HAS NOT PRODUCED RESULTS THAT WOULD WARRANT ADDITIONAL REGULATION. VOLUNTARY GUIDELINES SOON TO BE PUBLISHED BY THE ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION, WHICH WERE DEVELOPED JOINTLY BY PUBLIC-PRIVATE PARTICIPATION, APPEAR TO BE A STEP IN THE RIGHT DIRECTION.

MR. CHAIRMAN, WE CONSIDER THAT AMPLE EXPERIENCE EXISTS TODAY TO SUGGEST THAT NO HEALTH HAZARDS FOR DIALYZER REUSE HAVE BEEN DEMONSTRATED. WITH THE DEVELOPMENT OF REVISED STANDARDS FOR THE REUSE OF HEMODIALYZERS PRODUCED BY THE NATIONAL KIDNEY FOUNDATION AND THE NEW AAMI GUIDELINES FOR THE PROPER REPROCESSING, RESTERILIZATION AND REUSE OF DIALYZERS, ADEQUATE SAFEGUARDS WOULD EXIST TO ASSIST THOSE WHO PRACTICE REUSE IN ASSURING THE SAFETY OF BOTH PATIENTS AND STAFF. HOWEVER, IN ORDER TO ASSURE THAT ALL EXISTING SCIENTIFIC INFORMATION IS THOROUGHLY CONSIDERED, THE ACTING ASSISTANT SECRETARY FOR HEALTH HAS DIRECTED NCHSR TO COMPLETE A FORMAL ASSESSMENT WITH RESPECT TO SAFETY, EFFICACY AND COST-EFFECTIVESS OF DIALYZER REUSE.

MR. CHAIRMAN, THIS IS THE END OF MY FORMAL STATEMENT. MR. VILLFORTH AND I WOULD BE PLEASED TO RESPOND TO ANY QUESTIONS YOU OR OTHER MEMBERS OF THE COMMITTEE MIGHT HAVE.

Dr. **MARSHALL**. We will just summarize it a bit and then we can get on with whatever questions you may have.

The issue of first use versus reuse is one that has been around for a long time, since 1963, and there have been observations with respect to the advantages and disadvantages of both and the benefits that might accrue from both. These are issues that we probably will want to revisit some in the question period, although you have covered them somewhat with some of the other witnesses.

Our view, to summarize it, is that while we neither advocate nor oppose use or reuse, we do observe that it is safe and efficacious, and we base that not on controlled clinical trials, but on the extent to which it has been used and on the low incidence of reports of problems with it when the proper procedures for reprocessing the dialyzer are observed.

The observation that has been made, that I would reinforce, is that the growth of reuse has been very dramatic from 1980 to the present so that we are now in a situation where about 56 percent of the centers and 65 percent of the patients who are dialyzed in this country are dialyzed in settings where they are reusing the filters.

In spite of that phenomenal growth, the mortality and morbidity rates for dialysis patients have remained amazingly constant over that time.

Chairman **HEINZ**. What is your basis for that statement?

Dr. **MARSHALL**. For which statement, Senator, that the——

Chairman **HEINZ**. That the morbidity and mortality rates have remained constant? What is the basis for that statement?

Dr. **MARSHALL**. Reports in the literature and lack of reports in the literature.

Chairman **HEINZ**. Well, we had a report earlier today from a witness, Dr. Shuman, that the morbidity and mortality rose markedly at a clinic in Baton Rouge, LA.

Dr. **MARSHALL**. Well, that was an isolated instance, I think, and we will speak to that in a bit. I think we have looked at the details of that——

Chairman **HEINZ**. Well, let me understand——

Dr. **MARSHALL** [continuing]. And that was——

Chairman **HEINZ**. Dr. Marshall, just let me understand. You are saying the literature and I am asking you: What literature?

Dr. **MARSHALL**. The journals in which——

Chairman **HEINZ**. What journals?

Dr. **MARSHALL**. The nephrology journals.

Chairman **HEINZ**. I would appreciate the specific citations.

Dr. **MARSHALL**. We would be glad to——

Chairman **HEINZ**. Can you cite one study——

Dr. **MARSHALL**. Yes.

Chairman **HEINZ** [continuing]. One specific study?

Dr. **MARSHALL**. Yes; the 1986 study published by Pollack, which was described——

Chairman **HEINZ**. Which one?

Dr. **MARSHALL**. It was described by Dr. Wolf as lacking in scientific controls.

Chairman **HEINZ**. Which one?

Dr. **Marshall**. The Pollack study which appeared in January 1986. It compared 1,300 patients over a 7-year period in two dialysis centers. It is the one that you discussed with Dr. Wolf a few minutes ago.

Chairman **Heinz**. Dr. Beall.

Dr. **Marshall**. Oh, OK. I could not always tell from the back of the room who you were talking to about which one.

Chairman **Heinz**. Dr. Beall. Is that the only study you can cite?

Dr. **Marshall**. That is the most recent one. We can provide additional ones for the record.

Chairman **Heinz**. I just want to understand. Is there another study that you can cite?

Dr. **Marshall**. I don't recall which it would be. I would also look at the mortality——

Chairman **Heinz**. Please proceed. I am sorry for interrupting you.

Dr. **Marshall**. OK.

I would like to summarize a chronology of some of the efforts of the Public Health Service in support of the end-stage renal disease program that pertain to this particular issue.

In 1977, the Food and Drug Administration did issue guidance, which they revised in 1981, with respect to conditions under which reprocessing of these devices could be presumed to lead to a satisfactory conclusion. In 1979 and in 1980, a study was undertaken which has also been referred to here—the NIH study or the Deane study, however you wish to characterize it—which was intended to obtain information on procedures for multiple use.

Again, the finding was that depending on the adequacy of the reprocessing procedure, there was equivalent functional capacity found there.

In 1980, the Food and Drug Administration did a problem assessment study and they found, in that study, that there was no greater risk for patients for whom the dialyzer was reused.

In 1981 and 1982, the predecessor to my organization, the National Center for Health Care Technology, as one of its dying acts as it was going out of business, cosponsored with the Food and Drug Administration a public/private conference which yielded the first set of consensus guidelines with respect to reprocessing and reuse.

In 1982, the Assistant Secretary for Health, Dr. Brandt, established an end-stage renal disease strategic work group. That was followed by a 1983 Public Health Service end-stage renal disease coordinating committee.

The first of those committees recommended more study; the second of those committees did not except in the area of long-term effects; and both were in agreement that it would be good to have more data with respect to the long-term effects of dialyzer reuse.

CDC has been involved and their involvement became much more active following the 1982 episode to which you referred earlier in Louisiana where there was an outbreak in a center where 27 patients became infected and 14 of those patients died.

The problem there was clearly found to be one of contamination of the water supply by a nontubercular mycobacteria and that has led to CDC doing work, which led to identification of proper levels of disinfectant which could avoid that problem in the future; and there have not been subsequent outbreaks of that sort since 1982.

CDC has also continued, as has the Food and Drug Administration, to interact and consult and coordinate with national groups that were attempting to develop voluntary standards.

In 1984, the Centers for Disease Control, in conjunction with the Health Care Financing Administration's facility survey, surveyed a random sample of 115 centers. They found mycobacteria in the water supplies for 70 percent of the city water supplies that were being used and 48 percent of the water supplies of dialysis centers that had their own, but they only found three infected patients. This was considered by their epidemiologists to not be a significant rate of infection.

Again, I believe this suggests the safety of this procedure, when done properly according to the instructions and according to the state of the art, that is generally accepted.

They also looked at hepatitis rates and found no difference between single-use and multi-use centers in the rate of hepatitis, for either patients or staff, working in the dialysis center, and they are continuing to do that kind of survey and providing the feedback information to the Health Care Financing Administration.

The Food and Drug Administration has been interested not only in the reprocessing situation, because they recognize that there has been an increase in the use of reprocessed dialyzers, but they have been looking at other issues that are important for the safety of patients who were being subjected to this procedure.

These include the purity of water, mixtures of dialysates that are used, and temperature control during the process. Based on a study that they are presently supporting in three States and the District of Columbia, they are developing a comprehensive policy statement; and Mr. Villforth can speak in more detail to that if you would like to pursue that later.

In October 1985, the Health Care Financing Administration completed an agreement with the National Institute for Arthritis, Digestive Diseases, Diabetes and Kidney Disease to establish a registry. This registry for dialysis will make it possible to do long-range research as well as to provide patient and provider profiles.

HCFA's responsibility will be to provide the demographic and medical data, and to evaluate it; and NIADDK will do the biomedical and biostatistical analysis. This data base will allow us to look not only at dialyzer reuse, but at a number of other interrelated issues such as biocompatibility of blood products, machinery, and materials, the characteristics of various dialysates, determinates of long-term survival, acute-phase reactions, postdialysis syndromes, and access problems to the vascular system.

So we believe this to be an important piece of work that will provide an out-year knowledge base for adjusting policies if that proves to be necessary.

There is considerable interest in the question of the effects of the formaldehyde disinfectants which are most often used for reprocessing this equipment. The most recent CDC survey data suggests, of course, that formaldehyde is by far the most-used substance.

About a third of the centers are using a 4-percent solution; about a third of the centers are using a 2-percent solution; and about a third are using other concentrations or other disinfectants.

Part of the variation that we see and part of what the literature suggests is that the temperature at which you do the disinfecting makes a difference as does the use of certain other additives, such as ethanol. So it is an issue where I think we prefer to talk about procedures that are the equivalent of a 4-percent formaldehyde solution.

I think the state of the art in that is evolving. It is hard to say where we will go next with the use of things that might represent the best tradeoffs of safety versus hazard.

Chairman HEINZ. Let me interrupt.

Dr. MARSHALL. Sure.

Chairman HEINZ. When you use the term "state of the art," who is the artist?

Dr. MARSHALL. I think we are talking——

Chairman HEINZ. In medical practice, there are a lot of innovations, but the innovations are always limited, at first, very carefully: doctors who want to perform certain kinds of new procedures are licensed with the Food and Drug Administration with an experimental identifying number to do certain kinds of operations until they are found to be safe and effective.

Indeed, that is one of the principal standards that we use: safe and effective.

Is there a process by which people who are experimenting on patients are, in fact, licensed to perform those state-of-the-art experiments?

Dr. MARSHALL. That depends on the circumstances under which they are——

Chairman HEINZ. Well, in the case of reuse of kidney dialysis medical equipment. Is there any supervision or license, or is anybody licensed?

Dr. MARSHALL. It is my understanding that that is probably not well supervised—Dr. Villforth can speak to that in more detail—but basically——

Chairman HEINZ. Well, just so we understand what the term "state of the art" means. It means, in this case, that these people are experimenting on other people without supervision.

Dr. MARSHALL. I think it means both things.

Chairman HEINZ. That is a funny term. To me, that is not art.

Dr. MARSHALL. Well, you would probably also agree it is not science, either, necessarily——

Chairman HEINZ. Certainly, we do lack in that regard as well.

Dr. MARSHALL [continuing]. But it is better than voodoo because people will experiment within limits with changing the mix, changing the temperature, and see what happens. Practitioners do that all the time and there is not much of a way you can control it.

I think if they were using new equipment or using a complete new substance, then that comes under the statutes regulating those things. Then they are likely to proceed with approval and formal review of protocols; but maybe you could speak to that.

Mr. VILLFORTH. Well, I think the type of thing you might be talking about comes under the practice of medicine, which would not fall under the Food and Drug Administration's regulatory responsibility for devices.

Chairman HEINZ. Just so I understand your comment, what does washing devices have to do with medical practice?

Mr. VILLFORTH. Well, let me say washing of devices does not have anything to do with the manufacturing of devices. That latter is the responsibility of the Food and Drug Administration.

Chairman HEINZ. Well, that is what we are talking about, isn't it?

Mr. VILLFORTH. It is not the responsibility of the Food and Drug Administration how the physician cleans the tools that he or she uses.

Chairman HEINZ. Let me just ask something about that.

What are good manufacturing practices all about?

Mr. VILLFORTH. Good manufacturing practices are the procedures that we have developed and published in the Federal Register designed for manufacturers to help them produce quality products. They are directed at the manufacturing of medical devices.

Chairman HEINZ. Would you care to recite what the definition is of a "manufacturer" in the statute?

Mr. VILLFORTH. Well, the manufacturer includes all of those obvious things that we understand, such as the factories that make it and produce devices. The definition can be extended to people——

Chairman HEINZ. How about what it says as opposed to whether it is extended or not?

Mr. VILLFORTH. I cannot quote you the definition of what it——

Chairman HEINZ. Well, let me quote it to you——

Mr. VILLFORTH. Fine.

Chairman HEINZ [continuing]. Because it includes remanufacture. It says:

> Any person, including any repacker or relabeler, who manufactures, fabricates, assembles or processes a finished device.

Now, is somebody who is taking that equipment and washing it in formaldehyde solution processing that device? It is a finished device, is it not?

Mr. VILLFORTH. We have not in the past considered that to be manufacturing or remanufacturing under the intent of the medical device amendments.

Chairman HEINZ. That is not what the statute says. The statute says "* * * who manufactures * * *" a finished device, "fabricates" a finished device, "assembles" a finished device, "* * * or processes a finished device." It does not say it has to be processed by the manufacturer.

In fact, those are discreet terms and they are discreet for a reason: Because there are many stages and many hands through which a device may pass. Let me go on and just note that 21 CFR 820.155 states that:

> Reprocessing procedures shall be established, implemented and controlled to assure that the reprocessed device meets original specifications.

Now, you have just said that that is not your job. The statute says it is.

Who is right?

Mr. VILLFORTH. I have just said that it has been our interpretation in the past that we would not get into the practice of medicine as a clinician or a——

Chairman HEINZ. But this is not the practice of medicine. This is the reprocessing of a device.

Please don't try and wiggle off the hook.

Mr. VILLFORTH. I am trying to describe how we have treated this, in the past, as the practice of medicine. We are examining the question of whether reprocessing by medical institutions or commercial firms in connection with kidney dialysis would fall under the definition of our act.

We have opinions on that. The general counsel has reviewed——

Chairman HEINZ. You know, I hear what you are saying and I appreciate it; and thank God you are saying, "Well, we are taking a second look because we might be wrong."

Let me just also add, though, that when you say—and as the record will be for everyone including the general public to see—that, "Well, we have been considering this as medical practice," which sounds and implies that it is a doctor operating in the operating room on the patient having to make real-time decisions about what to suture and what to cut and what to clamp, it is going to look pretty ridiculous.

Can you not just say, in English, "Look, we overlooked this"?

Mr. VILLFORTH. No; I don't——

Chairman HEINZ. "It is time we got serious about it. We are sorry." Or is that unreasonable for me to expect a plain English answer?

Mr. VILLFORTH. I can appreciate what you are saying. Let me explain about good manufacturing practices before I answer that question of how guilty we are, if I may.

Chairman HEINZ. Why is it so hard to get a straight answer?

Mr. VILLFORTH. Because the good manufacturing practice regulation, as written, is a very general kind of a thing, but specific for the manufacturer. The mere fact that we would somehow include this type of a process under the definition would not be very useful.

We would have to go back and go into a lot more detail. We would have to develop—and we probably could, some very specific applications to the kind of problem that has been described here under the GMP because I don't think the GMP, as written, is going to be very helpful for this particular application.

Chairman HEINZ. Now I think most of you have heard most of the testimony today, did you not, both of you?

Dr. MARSHALL. Yes.

Chairman HEINZ. Now, you are both reasonable men and would you not conclude that there are some problems?

Let me sharpen the question to this extent: That first it has been testified to that there are clinics reusing dialyzers, this device—the hollow-fiber kind—30, 40, and 50 times. That is true.

Do you maintain that that is safe?

Dr. MARSHALL. I do not think we can answer that question with a general statement. There might be situations where it could be safe and there might be situations where it would not be. I think you have to look at the data.

Chairman HEINZ. What does the data suggest?

Dr. MARSHALL. The data would suggest that that would probably be out at the outer limit of what is safe, but that is an interpretation.

Chairman HEINZ. Is that at the outer limit of what is safe?

Dr. MARSHALL. Right; at the outer limit or beyond it because there——

Chairman HEINZ. Or beyond it.

You are not a medical doctor.

Dr. MARSHALL. I am not a physician; no, sir.

Chairman HEINZ. If it is at or beyond the level of what is safe, should not someone who is paying for it—that is Mr. Fleming at the Health Care Financing Administration—someone who is regulating it from the Public Health Service, should not someone in Government who is paying for it and who the taxpayers are paying to regulate it for safety and effectiveness be doing something about this?

Dr. MARSHALL. It seems to me that the person who is responsible for that should be the physician who is responsible for that patient's dialysis, and if that patient is not showing adverse clinical effects then I don't think there is a problem that you ought to address.

Now, when I made the statement——

Chairman HEINZ. Now, if the clinic says to the patient, "We don't care if you don't feel good," or "if you break out," or "if you bleed," or "if we have to increase your dose of heparin two or three or four times to 15,000 units three times a week when you come in here, that is tough. If you don't like it, you can go from Baton Rouge three times a week down to New Orleans," is that the way we ought to kind of just sit back and relax——

Dr. MARSHALL. No; that is——

Chairman HEINZ [continuing]. And say, "That's the marketplace of medicine."

Dr. MARSHALL. I am not making an argument for doing that. I am not suggesting that is appropriate.

Chairman HEINZ. Well, that is what is happening. What do we do about it?

Dr. MARSHALL. Let me try to answer the questions in sequence and try to clarify what I said about outer limits. The statement I made about outer limits was a statement derived from engineering models of what the decay function and the filtering capability of the device is likely to be; and that is why I qualified that by saying that might well be at or beyond the outer limits for what would be safe from an engineering perspective.

If a patient is showing that kind of adverse reaction, then I think that is a medical issue and it is not ethical medical practice to ignore that. Now, there may be a problem there in the communication or a conflict of interest between the physician who is responsible for that patient's monitoring and those people who are operating the dialysis center, but that is a whole different issue.

It is an important issue and it is one that needs to be addressed, but it needs to be addressed in the context of the quality of medical care.

Chairman HEINZ. Let me ask you a hypothetical question.

Suppose the Government, suppose Mr. Fleming at the Health Care Financing Administration—we will get to your testimony eventually, Mr. Fleming—which is very concerned about saving money because they pay all the bills says that they are going to reduce the reimbursement rate per treatment by about $10: Such regulations are being considered.

Does that not force reuse? Don't we know pretty well that if they cut that everybody will have to go to reuse and that the people who do only first-use will go out of business? Don't we have a pretty good sense of that?

If that were to happen, would Government not be preempting the choice of the doctor that you say the doctor should make?

Dr. **Marshall.** Let me give you a somewhat-hypothetical answer to that.

I don't think we know what that effect would be at this point because the data that I have reviewed on dialyzer reuse and relative costs suggests that for some centers, depending on the size of the center and the number of patients they have, it may be economically more feasible for them to use a new one each time. This is because, as one of the earlier witnesses observed, the cost is coming down for the purchase and the personnel costs for reprocessing are going up.

Those curves appear to be getting very close together and they may well cross at some point. So, we may be at a situation where what would drive that would be the relative size of the clinic.

I think the other part of that probably Mr. Fleming should respond to even though it is not his turn, but he has been waiting patiently, I know.

Chairman **Heinz.** He has.

Let's, at this point, give Mr. Fleming his opportunity to testify.

Mr. Fleming, thank you for being so patient. If you would like to give us your opening statement, we would be pleased to hear it.

Mr. **Fleming.** Mr. Chairman, before I give my testimony, perhaps I might just respond to the question of whether or not it would necessarily force reuse.

First of all, the regulation is only in a consideration stage. If it is published, it would be published as an NPRM and there would be ample time for all interested parties to comment on it. Then we would look at the comments and make a determination as to what to do.

As to whether or not a $10 reduction would necessarily force reuse, I don't think that can be stated for certain. We estimate that about 25 percent of the reimbursement cost is in supplies. The dialyzer itself would be something less than that.

Labor, alone, is about 36 percent, administration and general expenses about 21 percent of the cost, laboratory and drugs about 7 percent. So there are other areas where a center could look for economies if that were to come about.

Chairman **Heinz.** We both understand that the reimbursement rate has been based, up until 2 years ago, on a cost-based method of reimbursement, which agency has been very careful for the most part about scrutinizing and paring down and being very accurate. Although inflation has not risen as rapidly as previously, nonetheless, (a) it still exists and, (b) in health care there is more of it than anyplace else, unhappily.

Notwithstanding your tender ministrations of the Health Care Financing Administration—and this is not entirely your fault, of course; it may not even be your fault at all—that $130 rate has been around for a number of years. It is $131 for hospitals and $127, I think, for clinics.

A dialyzer costs anywhere from $10 to $13 depending on use. I guess the key question is: Is there a lot of fat in here? I don't think that even you would contend there is a lot of fat because for you to contend that would suggest that HCFA has not been doing its job.

Mr. **Fleming**. Senator, on the issue of the rates, what we try to do at HCFA is reflect the current practice, pull together the composite elements of the practice—in this case of ESRD treatment—and then the rates simply reflect that practice.

Chairman **Heinz**. Well, please proceed with your testimony, Mr. Fleming.

STATEMENT OF BARTLETT S. FLEMING, ACTING DEPUTY ADMINISTRATOR, HCFA, WASHINGTON, DC, ACCOMPANIED BY CHUCK BOOTH, OFFICE OF REIMBURSEMENT POLICY, HCFA

Mr. **Fleming**. Thank you very much. We share a mutual concern, obviously, for the health and the safety of Medicare beneficiaries that are served through the Medicare ESRD Program. The Health Care Financing Administration's role in the ESRD Program is that of ensuring safe and effective and efficient methods of treatment for all beneficiaries involved.

At the present time, we believe the question of reuse of dialyzers and other disposable hemodialysis devices to be a medical practice issue which should be decided by the patient's physician. Our current ESRD reimbursement methodology does encourage facilities to operate more efficiently, which, in some facilities, may prompt an increase in the reuse of disposable hemodialysis devices as a choice of one choice among several possibilities.

However, the decision to reuse should not take place until the physician first determines that it is medically appropriate for his or her patient.

Before I discuss the reuse of disposable hemodialysis devices more fully, let me first provide you, Mr. Chairman, with some of the background of the ESRD Program to put this in perspective.

As you are aware, with the enactment of the Social Security Amendments of 1972, Congress extended Medicare coverage to most people suffering from end-stage renal disease. Coverage began on July 1, 1973. Since that time, the most significant change in the program has been through the ESRD Program amendments of 1978, which were designed to promote efficiency and economy in the delivery of services by encouraging home dialysis and transplantation.

Since the implementation of the original ESRD law, the program has experienced rapid growth both in the population served as well as in program costs. In 1974, the first full year of operation, Medicare expenditures for 16,000 beneficiaries covered under the program were about $250 million; 10 years later, in 1984, over 78,000 beneficiaries received dialysis treatments and another 7,000 received renal transplants.

Chairman HEINZ. Mr. Fleming, I apologize. Those five lights and those five bells mean that I have less than 7 minutes to go and vote.

Mr. FLEMING. Let me dispense with my remarks.

Chairman HEINZ. No; don't. I must go and vote. I can be back in about 6 or 7 minutes if you will bear with us, and I hope you will.

Mr. FLEMING. Certainly.

Chairman HEINZ. The hearing is recessed for approximately 7 or 8 minutes.

[A brief recess was taken.]

Chairman HEINZ. The hearing will come to order.

Mr. Fleming, please proceed.

Mr. FLEMING. Thank you, Mr. Chairman.

To achieve the goals of the original ESRD legislation, the Secretary is given broad authority to establish requirements and regulations in connection with payments for dialysis and transplantation services under Medicare. The law and regulations also contain specific requirements that must be met by approved providers or renal dialysis facilities that enter into agreements with the Secretary to provide dialysis services.

For example, the facility must have a written long-term program representing the selection of a suitable treatment modality and dialysis setting for each patient to be reviewed and revised as necessary by a professional team comprised of appropriate medical personnel and the physician/director of the dialysis facility.

A patient care plan must also be developed which reflects the psychological, social, and functional needs of the patient, and indicates the care required and the methods to reach long- and short-term goals.

State health agencies under contract with HCFA survey and certify all ESRD facilities within their jurisdictions. Periodic Federal monitoring surveys are a backup check to this procedure.

The survey process has been very effective since it began shortly after the enactment of the ESRD Program. Surveyors review all facilities for compliance with regulations and, when deficiencies arise, appropriate actions are taken including termination from the program if necessary.

State surveyors also check Medicare facilities that reuse disposable hemodialysis services to determine if these facilities are, in fact, following a written policy covering the number of times dialyzers can be safely reused including procedures for the cleaning, sterilizing, and storage of those dialyzers.

One last area of background discussion that I think is necessary before we get into the issue of reuse is that during the first decade of the program's existence Medicare provided reimbursement to hospital-based facilities on the basis of reasonable costs for dialysis treatments, and to freestanding facilities on the basis of reasonable charges, subject to a payment cap.

Faced with rapidly increasing program expenditures, Congress, through the ESRD Program Amendments of 1978 and the Omnibus Budget Reconciliation Act of 1981, authorized the establishment of an incentive reimbursement system to encourage more cost-effective delivery of services, consistent with quality care.

In 1983, therefore, a new reimbursement system went into effect whereby facilities were paid on a prospective basis for treatment. This payment rate, or composite rate as it is known, is calculated based on cost reports of hospital based and freestanding dialysis centers weighted by average of facility mix.

Under current national average rates, freestanding facilities are paid about $127 per treatment and hospital-based facilities are paid $131 per treatment with adjustments as appropriate to reflect area wage rates.

The current composite rates are based on a 1977-78 survey of dialysis facilities' costs which, at that time, indicated a facility reuse rate of 11 percent. As part of our 1987 budget, we are proposing that the composite rates be adjusted to reflect current operating practices in the dialysis industry.

Our proposed rates will be based on a 1982-83 national survey of facilities' costs which indicate that approximately 50 percent of facilities were practicing the reuse of disposable hemodialysis devices.

Mr. Chairman, now that I have provided you with some of the background on the ESRD Program and our composite rate payment structure, let me discuss the reuse of dialyzers.

First, I would like to note that the reuse of dialyzers is not a new practice. In fact, reuse or the practice in which hemodialyzers are used for multiple dialyses without a replacement of membranes or other surfaces in contact with the blood, has been practiced since the early days of the dialysis era.

In these early years, reuse was a generally common and accepted practice. With the passage of the 1972 law extending Medicare coverage to ESRD patients, the practice of reuse declined brought about by an increase in the availability of improved dialyzers at a lesser cost and the advent of cost-based reimbursement.

In recent years, there has been a renewed interest and, indeed, a growth in the reuse of disposable dialyzers, as I mentioned earlier. This increase has most likely been motivated by two factors. First, clinical data show that the reuse of dialyzers is safe and effective when they are properly reprocessed; and, second, facility incentives to reduce health care costs.

As you are aware, the safety and efficacy of reuse has been a topic of intense debate and concern for some time. These concerns prompted Congress to mandate a study of the issue as part of the ESRD Program Amendments of 1978. The National Institutes of Health commissioned a study in this area and, in 1982, they concluded that reuse was safe and effective given that proper cleaning methods were employed.

These positive results have been supported by other professionals, in particular those who attended the 1984 International Conference on Disposable Medical Devices.

It should also be pointed out that the first use of hemodialyzers is not free of medical complication. That has been discussed today already.

Since the ability to treat with reused dialyzers varies considerably with patients, our position is that the physician must first decide if reuse is appropriate based on the medical condition of the patient being treated. In short, then, we regard reuse as a medical practice decision and this policy rightly preserves the Government's role as outside the practice of medicine while, at the same time, encouraging efficient operation of the ESRD Program.

I believe, Mr. Chairman, that the ESRD Program in general is operating efficiently and effectively. Over the years, the program has experienced many positive changes and improvements, such as the increased physician/patient choice regarding treatment setting and modality.

We will continue our efforts to assure that ESRD services are provided in the most cost-effective manner possible without sacrificing the safety and quality provided to patients.

I would be happy to answer any questions.

[The prepared statement of Mr. Fleming follows:]

Prepared Statement of Bartlett S. Fleming

INTRODUCTION

Mr. Chairman and members of the Subcommittee, I am Bartlett S. Fleming, Acting Deputy Administrator of the Health Care Financing Administration. I am pleased to appear before you today to discuss Medicare's policy regarding the reprocessing and reuse of disposable hemodialysis devices in the End Stage Renal Disease (ESRD) program.

Mr. Chairman, we share a mutual concern for the health and safety of Medicare beneficiaries being served through the Medicare ESRD program. The Health Care Financing Administration's role in the ESRD program is that of ensuring safe, effective, and efficient methods of treatment for all beneficiaries involved. At the present time we believe the question of reuse of dialyzers and other disposable hemodialysis devices to be a medical practice issue which should be decided by the patient's physician. Our current ESRD reimbursement methodology does encourage facilities to operate more efficiently, which in some facilities may prompt an increase in the reuse of disposable hemodialysis devices as one choice among several possibilities. However, the decision to reuse should not take place until the physician first determinesd that it is medically apropriate for his or her patient.

BACKGROUND

Before I discuss the reuse of disposable hemodialysis devices more fully, let me first provide you with some background on the ESRD program. As you are aware, with the enactment of the Social Security Amendments of 1972, Congress extended Medicare coverage to most people suffering from end stage renal disease. Coverage began on July 1, 1973 and since that time the most significant change in the program has been through the ESRD Program Amendments of 1978 which were designed to promote efficiency and economy in the delivery of services by encouraging home dialysis and transplantation.

UTILIZATION AND COSTS

Since the implementation of the original ESRD law, the program has experienced rapid growth, both in the population served and in program costs. In 1974, the first full year of operation, Medicare expenditures for 16,000 beneficiaries covered under the program were $250 million. Ten years later, in 1984, over 78,000 beneficiaries received dialysis treatments, and another 7,000 received renal transplants, with a total cost of over $1.8 billion.

SURVEY AND CERTIFICATION

To achieve the goals of the original ESRD legislation, the Secretary is given broad authority to establish requirements and regulations in connection with payments for dialysis and transplantation services under Medicare. The law and regulations also contain specific requirements that must be met by approved providers or renal dialysis facilities that enter into agreements with the Secretary to provide dialysis services. For example, the facility must have a written long-term program representing the selection of a sutiable treatment modality and dialysis setting for each patient, to be reviewed and revised as necessary by a professional team, comprised of appropriate medical personnel and the physician-director of the dialysis facility. A patient care plan must also be developed, which reflects the psychological, social, and functional needs of the patient and indicates the care required and the methods to reach long-term and short-term goals.

State health agencies, under contract with HCFA, survey and certify all ESRD facilities within their jurisdictions. Periodic Federal monitoring surveys are a backup check to this procedure. The survey process has been very effective since it began shortly after enactment of the ESRD program. Surveyors review all facilities for compliance with regulations and when deficiencies arise, appropriate actions are taken, including termination from the program if necessary. State surveyors also check Medicare facilities that reuse disposable hemodialysis devices to determine if these facilities are following a written policy covering the number of times dialyzers can be safely reused, including prodecures for the cleaning, sterilizing and storage of dialyzers.

REIMBURSEMENT

One last area of background discussion is that of dialysis reimbursement. During the first decade of the program's existence, Medicare provided reimbursement to hospital-based facilities on the basis of the reasonable costs for dialysis treatments and to free-standing facilities on the basis of reasonable charges, subject to a payment cap.

Faced with rapidly increasing program expenditures, Congress, through the ESRD Program Amendments of 1978 and the Omnibus Budget Reconciliation Act of 1981, authorized the establishment of an incentive reimbursement system to encourage more cost-effective delivery of services, consistent with quality care. In 1983, therefore, a new reimbursement system went into effect whereby facilities are now paid on a prospective basis per treatment. This payment rate, or composite rate as it is known, is calculated based on cost reports of hospital-based and free-standing dialysis centers, weighted by average of facility mix. Under current national average rates, free-standing facilities are paid $127 per treatment and hospital-based facilities are paid $131 per treatment, with adjustments as appropriate to reflect area wage rates.

The current composite rates are based on a 1977-78 survey of dialysis facility costs, which at that time indicated a facility reuse rate of 11 percent. As part of our 1987 budget we are proposing that the composite rates be adjusted to reflect current operating practices in the dialysis industry. Our proposed rates will be based on a 1982-83 national survey of facility costs which indicated that approximately 50 percent of facilities were practicing the reuse of disposable hemodialysis devices.

DIALYZER REUSE

Mr. Chairman, now that I've provided you with some background on the ESRD program, and our composite rate payment structure, let me discuss the reuse of dialyzers. First I would like to note that the reuse of dialyzers is not a new practice. In fact, reuse, or the practice in which hemodialyzers are used for multiple dialyses without replacement of membranes or other surfaces in contact with blood, has been practiced since the early days of the dialysis ERA. In these early years, reuse was a generally common and accepted practice. With the passage of the 1972 law extending Medicare coverage to ESRD patients, the practice of reuse declined, brought about by an increase in the availability of improved dialyzers at lesser cost and the advent of cost-based reimbursement.

In recent years there has been a renewed interest and indeed a growth in the reuse of disposable dialyzers, as I mentioned earlier. This increase has most likely been motivated by two factors: Clinical data which show that the reuse of hemodialyzers is safe and effective, when they are properly reprocessed, and facility incentives to reduce health care costs.

As you are aware, the safety and efficacy of reuse has been a topic of intense concern for some time. These concerns prompted Congress to mandate a study of the issue as part of of the ESRD Program Amendments of 1978. The National Institutes of Health commissioned a study in this area and in 1982 concluded that reuse was safe and effective, given that proper cleaning methods were employed. These positive results have been supported by other health professionals, in particular, those who attended the 1984 International Conference on Disposable Medical Devices.

It should also be pointed out that the first-use of hemodialyzers is not free of medical complication. Some experts have even addressed the issue of patients who suffer from "new dialyzer syndrome", that is, respiratory distress, backache, chills, and so forth. Because of this syndrome, many facilities pre-cleanse the dialyzer before it is used for treatment.

Since the ability to treat with reused dialyzers varies considerably with patients, our position is that the physician must first decide if reuse is appropriate, based upon the medical condition of the patient being treated. In short, then, we regard reuse as a *medical* practice decision. This policy rightly preserves the government's role as outside the practice of medicine, while at the same time encouraging the efficient operation of the ESRD program.

CONCLUSION

In conclusion, I believe that the ESRD program, in general, is operating efficiently and effectively. Over the years the program has experienced many positive changes and improvements, such as the increased physician/patient choice regarding treatment setting and modality. We will continue our efforts to assure that ESRD services are provided in the most cost-effective manner possible without sacrificing the safety and quality provided to patients.

I will be happy to answer any questions that you may now have.

Mr. FLEMING. I would like to introduce Mr. Chuck Booth who is with the Office of Reimbursement Policy in HCFA. He is at the table with me to help answer questions of detailed reimbursement issues.

Chairman HEINZ. Very well.

Mr. Fleming, how long have you been with the Health Care Financing Administration?

Mr. FLEMING. Three years, Mr. Chairman, in June.

Chairman HEINZ. Three years. You have been the Acting Head of HCFA for how long?

Mr. FLEMING. About 5 weeks, I believe as Acting Deputy.

Chairman HEINZ. Now, in your testimony you point out, correctly, that renal dialysis facilities must agree to conditions of participation for the Medicare Program. We all know that virtually everybody who seeks dialysis is covered by the Medicare Program.

Mr. FLEMING. Yes, sir.

Chairman HEINZ. It does not just cover senior citizens; it covers everybody.

We have had testimony today that the notion of either informed consent or freedom of choice seems to be absent at a lot of clinics. What do you require as standards in your conditions of participation with respect to either informed consent or freedom of choice?

Mr. FLEMING. There is nothing in the condition regarding those issues, Mr. Chairman.

Chairman HEINZ. Now, let me see if I get this straight, then. The Department's condition is that a medical judgment is being made by doctors and that you don't want to interfere in that. Decisions are being made by clinics that you reimburse that the doctor prescribes that the patient go to the clinic.

The clinic is saying to the patient, "You have no choice. It is reuse here or don't come here." The doctor may or may not either know about that policy or agree with that policy.

Are you contending that doctors need to know not only what the policy is, but how a specific facility goes about disinfecting the dialyzer?

Mr. FLEMING. Mr. Chairman, yes, we are.

Chairman HEINZ. So, doctors now have to be experts on a variety of different kinds of medical equipment.

Now, I go to a general practitioner. If I should have kidney disease, the first judgment he would make would be whether I need to go to a nephrologist; but you don't have to go to a nephrologist to be treated with dialysis and a general practitioner has enough trouble keeping up with the new drugs that the FDA is licensing.

Does it seem at all unreasonable to you that a medical practitioner should be able to know, first, whether or not the dialyzer is being reused, whether or not the blood tubing is being reused, whether or not the transducer filter is being reused, whether or not those caps are being reused?

How is he to know that? Does that not seem a little unreasonable, that he should know the ins and outs of how a specific clinic operates?

Mr. **Fleming**. Senator, I am not a physician.

Chairman **Heinz**. I am not either.

Mr. **Fleming**. If I were a physician and responsible for the lives and welfare of my patients, I believe I would want to know that.

Chairman **Heinz**. And the physician would want to know all that while he is treating people who have heart problems, cancer problems? Are you saying that the physician should know how that hospital maintains all the equipment? He should know who handles that equipment in the hospital or clinic—and he may operate in a half a dozen or a dozen different places—he is supposed to know all that?

Mr. **Fleming**. Senator, given the concern that was pressed today, I would assume that patients are going back to their physicians and saying, "This is a real problem," and the physician being responsible for those patients, having taken his or her professional oath, I would think would want, posthaste, to find out exactly what was going on there and see if the treatment that was being utilized was commensurate with what that physician felt was a prescribed and correct course of treatment.

Chairman **Heinz**. Let's assume that it is really humanly possible for the average physician to do that. Let us make that assumption. I think it is a fairly shaky assumption, and let's assume it.

That physician is practicing medicine in Baton Rouge, LA, where there is exactly one dialysis unit. He has a patient that if she does not get dialysis she will die. He takes that patient to the clinic and the clinic says, "We would love to treat your patient," and he is smart enough to know that a clinic that reuses a dialyzer 40 or 50 times is going to inflict some serious side effects on his patient.

The clinic says, "Look, we are certified by the Medicare Program. We meet their standards of participation. We have our way of doing things and if you don't like it go to another clinic."

How is that doctor, who may have been actually allowed in the door to check how they do it, but I doubt it, supposed to deal with that problem? You are telling us that he is responsible for dealing with it?

Mr. **Fleming**. I think the same way that physicians relate to other practitioners in the medical community when there is a disagreement about prescribed treatments. They discuss it, they work through professional associations.

Chairman HEINZ. And the facility says, "We have discussed it. We have a waiting list. We don't need your business. Take them to New Orleans."

Mr. FLEMING. I am sure, Mr. Chairman, that there are backup hospitals which have dialysis treatment on emergency bases to take care of that patient until it is ironed out.

Chairman HEINZ. We know that there are an awful lot of facilities, more and more and more, that are reusing. Some of them may be doing a good job reusing. Let's hope most of them.

But what about the ones that really are not and which people are really locked into? Are you saying that Government has no responsibility there? Because that is what it sounds like to me.

Mr. FLEMING. No; I don't think so.

Chairman HEINZ. Both you and Dr. Marshall, have stated with emphasis that for the Government to be doing anything would be to intrude on the sacred area of the way a physician practices medicine.

Now, what I have described is a limitation imposed by others on the way either the physician practices medicine or the patient has choice; but let's take it one step further. The patient is supposed to have some say in these matters.

Let's assume we have a doctor who knows everything there is to know about all of that plus all the other things. Let's assume that the doctor is willing to fight the clinic. Let's assume that he wins and the clinic says, "Right, we will take this patient on your terms," and the clinic does take the patient originally on those terms.

Then 6 months or a year later, the clinic decides that they are going to do something different. They go up to the patient and they say, "Well, we have to do things differently." The patient says, "Well, I am going to see my doctor"; and they say, "Oh, if you complain about this to your doctor or anybody else, you are out."

Is that the doctor's problem?

Mr. FLEMING. I think it is time for the inspector general, then, Senator. I think it is time for the regional office to take a look at it and for our State survey and certification people to go in and see exactly what is being done there.

Chairman HEINZ. But under the conditions of participation there is nothing wrong with that.

Mr. FLEMING. Well, we have to look at the situation and see what is surrounding it. There may very well be. We require the centers to lay out the way they are going to apply the dialysis treatment and the way that they are going to clean the dialyzers.

It is very likely that a facility that is practicing that kind of a treatment or which has those kinds of treatment practices may not have the very best interests of their patients at heart. We may find some other areas where they have taken some shortcuts.

I think we would be very concerned about that condition. I also would like to say to you and to the witnesses that appeared on the first panel that we do intend to have our regional offices look at those situations which were reported this morning and see if there are any problems that need further investigation.

Chairman HEINZ. Let me ask you this, Mr. Fleming. Has HCFA provided specific standards to dialysis facilities on reprocessing and reuse of not only dialyzers but blood lines and other disposable devices?

Mr. **Fleming**. I don't believe so, Mr. Chairman.

Chairman **Heinz**. Now, you have provided State survey and certification agencies with guidelines to ensure that clinics have appropriate written procedures governing reuse and reprocessing. Is that right?

Mr. **Fleming**. That is correct, Mr. Chairman.

Chairman **Heinz**. I am a little puzzled by that. On the one hand, you say it is the doctor's business. On the other you say, no, it is not the doctor's business. You have to have standards irrespective of what the doctor thinks.

I don't understand that.

Mr. **Fleming**. Mr. Chairman, I don't see that being in conflict. What we are saying to them is that in order for you to provide this service to Medicare beneficiaries we have to be sure that you are organized and professional.

To do that, we are going to look at your written standard operating procedures. We are going to be sure that you have them and that they are reasonable.

Chairman **Heinz**. Now, as I understand it—and tell me if I'm wrong——

Mr. **Fleming**. And that you follow them, Mr. Chairman.

Chairman **Heinz**. Pardon?

Mr. **Fleming**. Not only that they are reasonable, but that you follow them; not just that they are written down, but that you follow your own procedures that you have written down on paper that you said you are going to use in treating your patients.

I am sorry to interrupt.

Chairman **Heinz**. Now, Mr. Fleming, is it not the case that your agency has not yet formulated policy and standards on reuse because HCFA is waiting for FDA to formulate its policy and standards? Is that not the case?

Mr. **Fleming**. Not exactly. We have not formulated any standards because we do believe it is up to the practice of medicine. Clearly, if the FDA formulated standards—and I understand that a private organization, the Association for the Advancement of Medical Instrumentation, is in the process of doing that very thing—we would trust that once that happens that then the medical community would fall into line and regulate itself.

If that failed to be the case, then we would ultimately probably have to take a second look at it.

Chairman **Heinz**. So what you are really saying is that you don't maintain, philosophically, there is something wrong here. It is just that FDA has not told you to do something here yet.

Mr. **Fleming**. No.

Chairman **Heinz**. If they tell you, you will do it.

Mr. **Fleming**. I think if the FDA said, "Here is a set of standards that need to be applied," we would then look at that in a policy-setting environment and say, "Is this something that we want to require as a condition of participation?"

Philosophically, I cannot tell you where we would come out on that. We would look at it from a policy perspective.

Chairman HEINZ. Have there been any instances of concern on the part of the State agencies that they are not getting the guidance they need from HCFA?

Mr. FLEMING. I cannot tell you that there has been. I am not aware of any.

Chairman HEINZ. Let me urge you to review correspondence that HCFA has had with the District of Columbia. I have a July 3, 1984 memo to HCFA concerning complaints from the District of Columbia—here it is—regarding the reuse of disposable dialysis blood lines.

The memo states that, "CDC does not have a reuse blood line policy. We feel that the health and safety issues involving reuse of the dialyzer are similar in this situation. There should be a national policy disposition regarding the reuse of blood tubing in order to ensure the protection of the health and safety of patients."

Do you or your associate, Mr. Fleming, know if this request was ever acted upon?

Mr. FLEMING. I cannot answer that, Mr. Chairman. I would be glad to furnish that to the record for you.

Chairman HEINZ. Could you let us know?

Mr. FLEMING. Certainly.

[Subsequent to the hearing, the following information was submitted for the record:]

The memorandum of July 3, 1984 was reviewed by components of HCFA's Health Standards and Quality Bureau (HSQB) and the Bureau of Eligibility, Reimbursement and Coverage (BERC). On August 28, we advised regional officials that it was HCFA's position that it was premature to consider any change in the regulations until the results of the Association for the Advancement of Medical Instrumentation project were available. However, all ESRD networks were asked to advise regional officials of any problems that arose because of reuse. At the same time, HCFA forwarded to all regional offices F.D.A. material on reuse. In addition, on October 22, 1984, in a memorandum directed to the Philadelphia Regional Office, we instructed regional officials to continue to verify that specific procedures for sterilization existed and to continue to report any incidents of potential problems.

Chairman HEINZ. I have another memorandum from August 1984, concerning policy guidance regarding the reuse of disposables for renal dialysis. The author, in the Office of Coverage Policy of your agency, wrote to your Office of Survey and Certification:

"Your memo mentioned the need for interim policy guidelines to address recent complaints about the reuse of dialyzers and bloodline tube sets." The memo goes on to say:

"It is premature to consider any change in the regulations, as you suggest, until the results of the Association for the Advancement of Medical Instrumentation project are evaluated."

Has there been any movement on this suggestion for interim guidelines?

Mr. FLEMING. The AAMI final report is due this summer. There was a draft report, I think, a year or so ago; but the final report is due and we are waiting to see what that report says, yes.

Chairman HEINZ. There was another letter from the District Government to HCFA in October 1985, about a year later. This memo reiterates the same concerns of a year before regarding "* * * the need for clear guidelines from HCFA on reuse. Federal ESRD regulations do not have clear guidelines on reuse so we are unable to enforce or persuade the facility to follow the Association for the Advancement of Medical Instrumentation or the Kidney Foundation.

"Per the District's letter of September 12, 1984, once again clear direction from HCFA is requested on the position of HCFA on reuse."

Was there any action on that letter?

Mr. FLEMING. I cannot answer, but I will provide it for the record, once again.

[Subsequent to the hearing, the following information was submitted for the record:]

The memorandum for the District Government of HCFA in October 1985 requesting a policy statement concerning reuse of hemodialyzers and blood lines was reviewed by Philadephia Regional Office. On November 26, 1985, regional officials responded by restating the HCFA position that it was premature to issue a policy statement. Surveyors were again instructed in the interim to verify that facilities had specific sterilization procedures.

Chairman HEINZ. In December 1985, HCFA responded to questions regarding the agency's policy on reuse by saying "The FDA is currently examining the AAMI recommended practice for reuse of hemodialyzers. When we receive the FDA comments, we will consider what steps, if any, should be taken by HCFA."

Now, it seems pretty obvious to me that there was not much of a policy in 1984 or 1985; and I gather at this point you still don't have a policy.

Mr. FLEMING. That is right.

Chairman HEINZ. You are still waiting. Is that right? OK.

I guess the bottom line is how far are we from a policy? If you have no policy, I don't see how we can assure patients that they are going to receive safe and efficacious dialysis therapy.

Mr. FLEMING. Well, I am not sure I would agree that we do not have a policy.

Chairman HEINZ. Maybe I misunderstood what you said a moment ago. You said you did not have a policy.

Mr. FLEMING. The policy is for HCFA not to interfere in the practice of medicine and prescribe practice procedures for physicians and people providing this service.

We don't know yet what AAMI, FDA, and others are going to say in terms of the need for such a policy. When we hear that, then we will respond to it, Mr. Chairman.

[Pause.]

Chairman HEINZ. I have here HCFA Form 3427. It is a lengthy check list for nursing home inspection and concerns certain standards that must be met. For example, here is a standard under patients' rights in the Federal Code of Regulations, 42 CFR 405.2138, subparagraph (b):

"All patients are afforded the opportunity to participate in planning their medical treatment." Does the testimony given earlier by panel I indicate that we are doing well in fulfilling this condition?

Mr. FLEMING. Mr. Chairman, I think there is a difference between participating in the planning of and the patient having the final say as to what the treatment will or will not be.

Chairman HEINZ. Is there a problem as you see it with a clinic saying, "You either do it our way or you die?"

Mr. FLEMING. Certainly.

Chairman HEINZ. When you only have one clinic in town—and, remember, there are only 1,200 clinics nationwide and we have many times that in the way of cities and towns—would you not say that that goes a little far beyond whatever interpretation you want to put into participation and planning?

I mean, there is no participation in anything under these circumstances.

Mr. FLEMING. Surely. I would not disagree with that. I would say that the option, though, is not to die: the option is to go to the local hospital, community hospital, that has the backup facilities to handle that.

Chairman HEINZ. If there is one. If they have a dialysis unit.

Mr. FLEMING. Certainly, in Baton Rouge I am sure there is one.

Chairman HEINZ. What about patients being treated with consideration and respect? That is covered by subparagraph (c) of 42 CFR 405.2138.

Mr. FLEMING. We have heard this morning circumstances that would lead us to believe people have not been considered in that way. That is why I said I would like to refer those cases to our regional offices to see if it warrants further investigation by us or even, perhaps, the inspector general's office.

Chairman HEINZ. And then there is a standard covering patient grievance, 42 CFR 405.2138, subparagraph (e): Briefly, it provides for a "grievance mechanism" under which patients can participate "without fear of discrimination or reprisal." Do you have any data from the State survey agencies with which you contract as to whether or not any of these standards for participation are being adhered to? Do we have information on this?

Mr. FLEMING. We can provide information, Senator, and I can say that we have had one center that has been terminated, 3 years ago I believe—I may be off in the number of years. Just 2 weeks ago, two facilities were given notices of termination and have since moved to change their practices in order to comply with the conditions of participation.

Chairman HEINZ. What standards of inspection do you have for the State agencies?

Mr. FLEMING. It would be in a State agency manual, Mr. Chairman.

Chairman HEINZ. You have no standards for inspection requirements. You pay them money to do this, but you have no standards for whether or not they should inspect and on what terms and conditions.

Mr. BOOTH. Well, Mr. Chairman, there is a whole manual of procedures that the State agencies are required to follow in their survey and certification process.

Chairman HEINZ. I am just asking, what are the requirements with respect to inspection?

Mr. BOOTH. They are required to periodically inspect ESRD facilities. They are required to inspect other health care providers, licensed as you put it, to deliver health services for Medicare beneficiaries.

Chairman HEINZ. What standards are they supposed to apply in inspections?

Mr. **Booth**. They are supposed to inspect the conditions of participation.

Chairman **Heinz**. Aha.

Mr. **Booth**. They are supposed to inspect to see whether or not the facility is meeting the conditions, some of which you have outlined.

Chairman **Heinz**. Well, I would be very interested in that information. I think a lot of the people who are kidney dialysis patients would like it, too.

Mr. **Fleming**. Let me restate, Mr. Chairman, if I may, though. We are equally concerned about it and, based on the testimony that we have heard today, we not only will be checking on those specific incidents, but redouble our efforts to communicate with our State contractors to ensure that these are being watched.

Chairman **Heinz**. I guess what worries me is that we know, according to recent-published reports, that there are 900 substandard nursing homes. Those facts have been around for a while, except they have not come to public light.

Now, for all we know, we have an equal or worse proportion of substandard dialysis facilities. I think the answer is nobody up here knows. Is that not right?

We don't know. We don't have the facts. The issue of substandard nursing homes has been around for decades. I mean, that has been focused on with spotlights and curtains going up and crashing of cymbals. That is not a new one for anybody.

If I had to guess, I would say you are probably in far worse shape with dialysis units than you are with nursing homes. I hope that is not the case; but after what I have heard today, I have every reason to believe it would be strictly luck, great luck if it were not the case.

Mr. **Fleming**. We have received lots of communications about nursing homes from patients and families of patients. I cannot tell you that we are inundated on ESRD issues.

We obviously get them and we check them out when we do receive them, and we want to know about them.

Chairman **Heinz**. Well, I would like just to get one other item here on the record for Dr. Marshall and also you, Mr. Fleming.

You have stated that the position of the department is that it is not opposed to nor does it advocate reuse of these disposable devices. That is up to doctors.

Just so we are clear, I would like to know your positions on the coercing and forcing of dialysis patients to reuse these devices and the even more outrageous practice of threatening patients with expulsion from the clinic if they do not submit to reuse.

Dr. Marshall, what is the position of the Public Health Service on that practice?

Dr. **Marshall**. I think we would say that when that occurs that represents a serious dereliction of duty on the part of the medical community.

Chairman **Heinz**. What should the Public Health Service do about it?

Dr. **Marshall**. I think that what the Public Health Service should do about it is to continue to educate the practicing community with respect to what are the best options, what are the standards of practice.

Chairman HEINZ. Your answer is, take this person who is derelict in their duty and educate them.

Dr. MARSHALL. No; well, that is the first part of my answer.

Chairman HEINZ. All right.

Dr. MARSHALL. The studies that we have show that a lot of the times when physicians do things that are considered to be not consistent with medical standards, it is because they don't know any better.

Chairman HEINZ. All right. They are derelict in their duty so you try and educate them; and then what? Do you have a no-pass/no play policy? [Laughter.]

Dr. MARSHALL. Well, historically the Federal Government has left that to the States. I think the second level of our effort ought to be—and I think that Mr. Fleming has already spoken to that—to be sure that the State survey agencies are aware of where there are changes in standards and what good practice is.

They have mechanisms for alerting them to things for which they should do better.

Chairman HEINZ. So the policy of the Public Health Service is let somebody else worry about it.

Dr. MARSHALL. It is that regulation of medical practice is most appropriately done at the State or local level; yes, sir.

Mr. FLEMING. Mr. Chairman.

Chairman HEINZ. Mr. Fleming.

Mr. FLEMING. Where we have found that to be the case, I would say it is intolerable and we would move, through the State survey and certification process, to find out if there are violations of conditions of participation; and, if that is the case, move to decertify the unit as an eligible facility to participate in the Medicare Program.

Chairman HEINZ. So your answer is if the State will tell us that there is a problem we will do something about it.

Mr. FLEMING. Mr. Chairman, it is a State's responsibility through the contract to do so. It is also the responsibility of citizens who are aware of problems to report those.

I would hope that our citizens would not be the least bit shy about contacting the Health Care Financing Administration and their Congressman who, I am sure, would in turn contact us and let us know so that we can follow up and investigate those charges.

When we get a report of a problem, such as you have described, we have the authority to go in on that problem.

Chairman HEINZ. I think if there was an effort being made to ensure that the people that you were contracting with, the State survey agencies, are in fact doing what you are paying them to do, I could really run up the flag and salute you.

Neither you nor I have much that we can put on the record as to our confidence that what you just described is, in fact, being carefully reviewed and looked at by the State and local agencies. So I am going to withhold running the flag up the pole and saluting. Right now, it is flying at half-mast.

Mr. FLEMING. Yes.

Chairman HEINZ. I want to come back to a line of questioning that I had with Dr. Marshall earlier which really disturbs me. I worry that when you take all the agencies down at DHHS—whether it is HCFA or the Public Health Service or the Food and Drug Administration or your center or NIH—that we have serious confusion on our hands; and that everybody is running around saying, "There is a problem, but it is somebody else's problem."

One of the specific laws we have on the books is the good manufacturing practices. I pointed out earlier to you, Dr. Marshall, that the citation I mentioned—which is 21 CFR 823(k)—defines a manufacturer as "* * * any person who processes a finished device * * *," and that 820.115 states that "* * * reprocessing procedures shall be established and implemented and controlled to assure that the reprocessed device meets original specifications."

Your answer to that was, well, this is neither.

Dr. **Marshall**. I believe, Mr. Chairman, that Mr. Villforth indicated that this was an issue that the FDA is considering and is willing to consider, and that—although he did not say it, I will say it—we will take your concerns and interests into account in doing that review.

But making that kind of analysis and translating that into policy is something that needs to be done in the context of a long history of how FDA's legislation has been interpreted both by the department's general counsel and by the courts; and those things really occur in that context.

But we will, in this specific instance, consider that as one of the issues to be addressed in our assessment of the situation at the present.

Chairman **Heinz**. I am kind of puzzled as to why there is so much disagreement over something that has been on the regulatory books since 1978. Is there an organization in the Public Health Service called the Reuse Committee?

Mr. **Villforth**. There is an organization within the Center for Devices and Radiological Health which is involved with reuse, yes, sir.

Chairman **Heinz**. You have a reuse committee at your Center.

Mr. **Villforth**. That is right.

Chairman **Heinz**. What is the position of the reuse committee on this issue?

Mr. **Villforth**. The committee has completed a document which suggests that we need to investigate the problem of expanding the definition of reuse to include reprocessing centers. That document has not been staffed completely within the Center. It is still in the draft stage and no final action has been taken on it.

But, yes, there has been the study and that is a preliminary opinion of that group.

Chairman **Heinz**. What is the position of the reuse committee on the Federal regulation that I just cited.

Mr. **Villforth**. You have the copy in front of you. I am not sure exactly what it says, but let me readdress the question of reprocessing you asked me earlier. Under 820.115—the good manufacturing practice regulation, the intent was directed to the reprocessing at the manufacturing level. It was not intended for the reprocessing as you describe here.

Processing and reprocessing refers to those kinds of products where sterilization or packaging is of concern in terms of a finished product. By this I mean a product not yet in commercial distribution that has to be resterilized as a result of its failing to meet some aspect of the good manufacturing practices, or if it had to be repackaged.

So the question of reprocessing came up in this context of the good manufacturing practices regulation. Although I understand the words that you read could be interpreted to that, I don't think it was originally intended to get into this question of getting the Food and Drug Administration into the practice of medicine. To put us in the operating room, so to speak, or to check on the physicians to see if they are resterilizing equipment properly, is not what is intended.

Chairman HEINZ. Has the reuse committee been around for a while?

Mr. VILLFORTH. For several years. I don't know how long.

Chairman HEINZ. Based on what you just said, one would be led to believe that any standardsetting for reuse of anything would have been considered by your agency and others intrusion into the practice of medicine that the doctor has a particularly hallowed place in practicing.

Is that the position?

Mr. VILLFORTH. From the standpoint of regulating the physician as a manufacturer.

Chairman HEINZ. Or how about regulating some other manufacturer besides the physician?

Mr. VILLFORTH. That is one of the concepts that the reuse committee has come up with, and we have to make a determination as to how far one goes into that practice of medicine versus commercial reprocessing firms.

Chairman HEINZ. You know, here is where the problem is. The problem is that that regulation has been on the books for 7 years.

Mr. VILLFORTH. Intended for manufacturers, yes, sir.

Chairman HEINZ. 1978.

Mr. VILLFORTH. Again, intended for the manufacturing of medical devices.

Chairman HEINZ. The same regulation that you are debating today has been on the books since 1978. You are saying, "Well, although we have been debating this for a while, we are finally now thinking about maybe possibly getting to a decision."

What you have described is a rationale—namely, this is strictly a physician area—in spite of the fact that you would have to be a total dolt, and you are not, to believe that a physician is going to be able in a dialysis clinic to understand what is happening to all of the elements of the equipment on that machine there.

Now, can you take that machine apart and put it back together?

Mr. VILLFORTH. No, sir.

Chairman HEINZ. Can you run it?

Mr. VILLFORTH. No, sir.

Chairman HEINZ. Do you expect a physician to be able to do that?

Mr. VILLFORTH. Yes, sir.

Chairman HEINZ. You expect him, a general practitioner, to be able to run that machine and take care of it and plug people in and clean all the equipment. You expect that of a general practitioner.

Mr. **Villforth**. I don't know about a general practitioner, but I would assume that the individual responsible for the dialysis clinic would understand the apparatus, as does an anesthesiologist who is responsible for anesthesia equipment and other professionals are responsible for the equipment they use.

Chairman **Heinz**. What you are saying is you are assuming that a third party—a third party: Not the physician who is treating the patient, a third party, a for-profit corporation, and I am not against for-profit corporations but it is still a third party—with other motivations is really interested in doing everything you have just described even if the doctor is powerless to ask them to do it.

Mr. **Villforth**. I don't know about the third party. I am assuming that a clinician is responsible for that particular operation. I am assuming that a radiologist is responsible for the radiology clinic and knows about the aspects of its equipment. And as I said, an anesthesiologist is responsible for the anesthesia equipment he or she uses.

Chairman **Heinz**. Well, let me tell you what the trouble is with the assumption. That assumption has kept the Public Health Service and your Center going round in circles for a number of years because it is a matter of common sense to, I think anybody—and I am not a doctor, but I know a lot of them and some of them still treat me and speak to me—realizes that what we have described today is just something you cannot rely upon a doctor to be intimately familiar with; what you have described as a reason not to adopt a policy.

I guess my question is: When are you going to adopt the policy?

Let me tell you what the reuse committee believes you ought to do for a reprocessed used device to be considered safe and effective. They believe that:

> The reprocessor must demonstrate that the device to be reprocessed has not been demonstrated to be a single-use device by the original manufacturer.

Now, we have had testimony that the manufacturers develop these tubes for single-use; they are not tested for multiple use. Right?

Mr. **Villforth**. That is right.

Chairman **Heinz**. That is why that is important, is it not, that if the manufacturers are making things that are only safe and effective for one use, that if they are used multiple times they may be unsafe. We have had some testimony that explains how they become unsafe.

They come apart; blood leaks out and air leaks in. I have not tried an injection of air in my bloodstream lately, but it is not good for you. Right?

Mr. **Villforth**. That is my understanding, yes.

Chairman **Heinz**. No. 2, "The characteristics of the reprocessed device is not altered by the reprocessing to such an extent that the device cannot be used by a patient in the manner intended by the original manufacturer."

The original manufacturer, I assume, who labels this clearly "single-use only" has the intent that his device do the job—namely, cleaning the toxins, salt, and water out of the blood of the patient—and that it reaches certain standards of effectiveness: 98 percent removal, whatever it is.

When a device falls to 80 percent efficiency or 40 percent efficiency, maybe that is a problem because the patient walks around sick and is likely to get sicker; and apparently some of them have.

So that is a problem, is it not?

Mr. VILLFORTH. It can be a problem, yes. Recognize, also, that we are coming from a situation where there is not a large record of problems with reuse. In fact there are some indications that it is better than single-use. The first-use syndrome is one.

The mortality and morbidity study done in 1976 and 1978 in the United Kingdom and in Europe suggests the mortality is lower in reuse patients.

Chairman HEINZ. Was there a clinical component to that study?

Mr. VILLFORTH. There was observation of patients in the clinic.

Chairman HEINZ. When I say a clinical component, what I mean is a clinical study. I am not an expert on research, but we all know that for studies to be meaningful you have to have control groups, you have to have a number of safeguards, you have to have——

Mr. VILLFORTH. The controlled clinical trial question that you are raising was not done in these sorts of studies.

Chairman HEINZ. All right.

Mr. VILLFORTH. These were patient observations, not necessarily——

Chairman HEINZ. Can one come to conclusions about safety and effectiveness without doing those kinds of clinical studies?

Mr. VILLFORTH. I think we have based our conclusions on the fact that there is a long——

Chairman HEINZ. I did not ask whether you had.

Mr. VILLFORTH. Yes.

Chairman HEINZ. I said can you come to sound conclusions about safety and effectiveness about any kind of medical procedure without clinical studies?

Mr. VILLFORTH. I think clinical medicine does.

Chairman HEINZ. No; I meant you.

Mr. VILLFORTH. The ideal, of course, is under controlled clinical studies. You are right.

Chairman HEINZ. Beg pardon?

Mr. VILLFORTH. I say you are right, in that the ideal way to do things is under controlled clinical studies. But those take time. We have a lot of history with the use of formaldehyde. There has been this information that we have reported.

I wanted to emphasize also that we have a device-reporting network, a device-experience network, and a medical-device-reporting network which reports to us problems—the device-experience network by clinicians, the medical-device-reporting network by manufacturers—with devices or problems with their use.

Over the 1 year that we have operated the medical-device-reporting network and several years of the DEN study, we have only about eight observations of problems with formaldehyde, as an example. Those problems have been clearly attributed to misuse on the part of the operators in which there were misconnections of water lines causing excessive doses of formaldehyde into patients.

These are serious problems—but we have not seen anything in the area of reuse.

So there are pieces of evidence that have come in that suggest that reuse has not been a chronic problem.

Chairman HEINZ. We keep talking about our knowledge of problems. First, we have established that we don't know the extent to which the State agencies are checking standards of participation, which we have been through—we just don't know—going to clinics and actually sampling and spot checking.

Let me ask, how many clinics has the Public Health Service, the FDA specifically——

Mr. VILLFORTH. Well, the Food and Drug Administration, as you know, has a study with four States—California, Ohio, Massachusetts, and the District of Columbia—in which we have asked State inspectors to go out into dialysis clinics.

Chairman HEINZ. But how many inspections has FDA done?

Mr. VILLFORTH. I don't think FDA has done very many other than to follow up particular complaints that might have been received about some problems. I don't have that exact number.

Chairman HEINZ. Could the number be three?

Mr. VILLFORTH. I don't know.

Chairman HEINZ. I think you will find, on checking, that it is. What we are really saying here is that we don't really have any information from the States that we can use.

Mr. VILLFORTH. As I said, have contracted with those four States to collect this information.

Chairman HEINZ. I am delighted to hear that you have. Let me read you something from 1980. This is an FDA paid-for report. I quote from page 344, and that is not all there is to this report. It goes on.

> C. Recommendations. The issue to be resolved is whether standards, whether performance or disclosure, can be written for the reuse of dialyzers. At the present time, such standards cannot be proposed for two reasons.
>
> First, in the absence of definitive studies the necessary criteria to establish standards cannot be formulated. Second, at the present time manufacturers label dialyzers as being intended for single-use only.
>
> Unless these issues are resolved, standards related to reuse are not relevant. No devices to accomplish reuse are commercially available in the United States. The development of such devices in the future will depend upon establishing reuse procedures proven to be safe and effective.
>
> Until that has been accomplished, proposal of standards is not indicated.

The inference, by the way, is that reuse is not justified.

Mr. VILLFORTH. I think the collaboration that we have had—the various Public Health Service agencies and with others on the AAMI reuse document, and prior to that on the AAMI standard, are indications of the need to get those procedures down.

As was said before, the hemodialysis reuse recommendations of AAMI should be out in a matter of months or this summer.

Chairman HEINZ. What you are saying is that something which was never contemplated—that is to say the reuse of those single-use-only piece of equipment—is presumed to be safe and effective until standards are set. That is what you have just described FDA policy as being.

Mr. VILLFORTH. FDA did not set policy on or require manufacturers to label products single-use or multiple-use.

Chairman HEINZ. I am not talking about labeling. I am talking about FDA findings, conclusions, recommendations.

The FDA, in 1980, was saying, these are single-use only. There is no basis for allowing them to be reused. Reuse standards are meaningless until it is found that reuse is safe and effective, and under what terms and conditions.

What you are saying is that the FDA's policy is where reuse is not contemplated and is not proven to be safe and effective it is all right for reuse to take place until some standards are established that prove that it is or is not safe and effective.

Mr. VILLFORTH. The purpose of the document that you have—the "Problem Definition Study," was to determine whether it was appropriate for the FDA to contemplate regulatory performance standards for the manufacturers. That is how that evolved.

The decision was that it is not appropriate for us to regulate the performance at the manufacturing level.

Clearly out of that emerged a concern about all aspects of hemodialysis, both in terms of reuse and some other aspects in which there have been problems, such as water supply monitoring and so forth, which are separate from the issue of reuse. We have seen deaths in those areas. We have had problems in other areas of hemodialysis separate from reuse.

So the question of the need for information to the medical community was raised. We determined that the best way and the fastest way to have that done was through the work of AAMI, a voluntary group.

Chairman HEINZ. Your other policy is that until a voluntary group establishes standards, that we need not have any.

Mr. VILLFORTH. No; that is not necessarily true.

We recognize it is a lot faster——

Chairman HEINZ. Is it true in this instance?

Mr. VILLFORTH. We feel it is a lot faster and a lot more efficient to use the voluntary standards route. We have encouraged that.

Our experience in the few areas where we have had regulatory performance standards for some radiation products—x ray machines, for example, is that for the nine different standards that we have promulgated, it took us an average time of something like 38 months, and that was in an environment when it was a little bit easier to get some regulations out. In addition to this, we have had to make an investment of about 40 person-years or full-time equivalents, to get each of these standards out.

Once those standards are out and we have to enforce them, it takes us another 23 person-years per year to enforce them. Establishing performance standards under the requirements of the Administrative Procedures Act and so forth is slow. They are thorough, and in fact, very resource intensive.

If we can accomplish the same goal through the consensus process, we encourage that process. Thus, the "Problem Definition Study," which you read from, resulted in feeding that information to AAMI and in AAMI developing the standard which was talked about earlier.

Chairman HEINZ. We have had testimony citing studies in 1980, 1981 several times over, 1982. It is 1986 and in spite of the fact that those earlier studies all said there is a need to find additional information, there is a need to have a variety of clinical studies so you can set standards, what you are saying is we have ignored all of that for 4 years; we do not have a policy today; and we are hoping to get one, hopefully some time soon, in the future.

Why have we delayed for a minimum of 4 years in coming to grips with this? Is it the budget? I mean, are people's budgets just being cut? Is that what it is?

Dr. **Marshall**. No, Mr. Chairman. Let me answer by trying to make a distinction, and that is a distinction between our position with respect to reuse and our position with respect to reprocessing.

We have talked about both of these, but I think we react differently to these issues. On the reuse, I think there has been clear, unanimous opinion that this procedure, reuse, is safe and effective if the reprocessing is done according to standards that are not perhaps as tight as some people would like them to be, but which are general and which are wellknown and have been communicated to the field.

There has been an effort—and it is a slow effort, but it is an effort that is close to coming to fruition—that will consensually validate those standards. The Government has participated with the private sector in that.

Now, I think that there is a principal reason why there has not been more of a sense of urgency and I will not hide behind the budget because I don't think it is primarily a budget issue, although that certainly impacts on it.

I think it is because as we have looked at the data there has not been a sense that there is a major problem out there. There are 78,000 people on dialysis at the present time and there is not evidence, as I indicated at the beginning, that there is an upward trend in mortality or morbidity.

There clearly are situations where clinics are not doing the right thing. We have heard testimony today of people who feel as if they have been coerced, and that is not acceptable.

Whatever the Federal bureaucracy's response to that might be a clinic that tells somebody "We are not going to treat you anymore" is subjecting themselves to criminal liability in terms of State statutes for abandonment and to civil litigation. I think that there are mechanisms that people ought to be able to use to pursue those that don't necessarily focus in Washington or Baltimore.

But I think the main reason why we followed a deliberate pace in this has been the absence of any kind of compelling evidence that there are serious problems. That is the same basis——

Chairman **Heinz**. If you don't have information, how can you have evidence?

Dr. **Marshall**. Mr. Chairman, I believe we do have information. We have information that there are lots of people being dialyzed—there has been a dramatic increase in the reuse of the dialyzers—and there have not been reports of untoward effects except in isolated instances.

Chairman **Heinz**. Let's get down to cases with what endstage renal disease is.

It is a condition that ultimately is going to shorten your lifespan substantially.

Dr. **Marshall**. Yes, sir.

Chairman **Heinz**. It would seem to me, particularly since there have not been controlled clinical studies done, that as you improve a technology with the improvement and more frequent use of that technology that, on the one hand, you will be helping people prolong their lives. So you have that particular trend going for you.

There was a time, back when I was a Member of the House of Representatives immediately before I helped write the legislation that created this program, that I remember visiting in the municipality of Avalon in my congressional district. There was a woman who could only go once or twice a week to be dialyzed, OK? Now, three times a week is standard practice.

At the same time, there are crosscutting trends, such as the one we are talking about, such that the studies you have, which are not clinical and carefully controlled, which show no increase in morbidity or mortality don't mean anything because there are other trends. This is precisely what clinical studies where you have careful control groups are meant to isolate, including even the bias of the observers who are doing the studies: the so-called doubleblind studies.

I must tell you, when you say there is no evidence, boy, I will tell you there is no evidence. There is no evidence that we have any facts at all.

To have people in our Public Health Service who I know are able and smart sit before this committee and say that, well, the evidence is that there is no problem, when the people sitting before this committee know just how statistics can be misleading is really shocking.

What do you have to say to that?

Dr. **Marshall**. Mr. Chairman, I have not said that there are no problems with either individual patients or that there are no problems with individual centers.

Chairman **Heinz**. I am not talking about individual patients. You know I am not talking about individual patients.

Dr. **Marshall**. Well, I am talking about the studies and the literature. There are a variety of forms of the scientific method and not every instance requires a carefully controlled, prospective, randomized, clinical trial.

Chairman **Heinz**. I think we all understand that. I will just quote something you said earlier, "Reuse is OK if it is done properly."

Dr. **Marshall**. That's right.

Chairman **Heinz**. If it is done properly. That is the big if, and that is what we have not looked at. That is what at least, at long last, you are beginning to look at.

I just hope that as a result of this hearing we will look not only at those standards, but we will look at the possible violations of the conditions of participation.

I commend you at least on one thing. You all agree it is wrong for patients to be coerced, and I think you all believe that we ought to do something about that: that there ought to be freedom of choice.

I think you are actually coming around to the point where you believe there ought to be standards to be consistent with your own regulations.

Dr. MARSHALL. I believe, Senator, we have always believed that there should be standards for the reprocessing. The question is whether they should be Federal regulations or whether they should be developed as voluntary standards with all of the parties who are at interest; and we have taken the position that the voluntary trend is the better one.

Chairman HEINZ. Now, as I understand, when you say "developed voluntarily by parties at interest," are you saying let every clinic set their own standards?

Dr. MARSHALL. No, sir; absolutely not.

Chairman HEINZ. But is that not present policy?

Dr. MARSHALL. Present policy is that there has to be a written policy for each clinic with respect to what standards they follow.

Chairman HEINZ. Right. Is that not letting every clinic set their own policy?

Dr. MARSHALL. I don't believe it is quite that freeform, Mr. Chairman.

Chairman HEINZ. Why is it not?

Dr. MARSHALL. Because all of those clinics are likely to be aware of what the standards of practice are that are considered acceptable in that particular business and they realize—if the operators don't realize, I am sure that their attorneys realize—that they are increasing their litigation risk if they have set a standard that is very much different from those that are considered to be appropriate.

Now, the Public Health Service ——

Chairman HEINZ. All of that may very well be true, but it still boils down to the same thing: they are responsible, it is freedom of choice for them in setting their own standards.

They may be aware; they may be ethical; or they may not care.

Dr. MARSHALL. The State survey agencies are kept abreast by the Centers for Disease Control, for example, of what the Centers for Disease Control find to be acceptable standards for the high level of disinfection that is necessary to maintain patient safety.

Chairman HEINZ. Dr. Marshall, I don't know why we are beating around the bush on this point. You can say that there are these pieces of information and this kind of education available, but the fact is—yes or no, please—that each clinic sets its own standards. All it has to do is write them up and hand them in to the State agency, and it has complied.

Is that not right?

Dr. MARSHALL. At one level, that is correct.

Chairman HEINZ. Well, I did not think it was that tough a question, but it proved to be extremely difficult.

I don't have any more questions right now. I may have a few more for the record. I appreciate your being with us today. You have been very patient.

I hope that out of this hearing there will be a heightened sense of urgency on a variety of fronts that we have mentioned. I think if we fail to take note of what is going on out there in the real world and we all hide here in Washington—it is all to easy to hide here in Washington—we don't advance our own careers; we don't advance the war against the budget deficit.

I mean, heavens, if people get sick and have to be hospitalized because we are allowing unethical providers, hopefully who are few, to reuse these devices, make people sick, have them go to the hospital, we know who pays for the hospitalization: the taxpayers, ultimately.

I was interested in the testimony of Dr. Oberley who had been on dialysis for a very long time and had only been in the hospital 4 days. I suspect there are a lot of people who have not been so lucky who may have gone to the hospital for far longer and more frequent periods because of the reuse of this equipment.

If economy is simply saving in one area and inflicting costs in another, that is a false economy.

So I thank you all. Mr. Fleming, welcome to your new job. Don't worry, it can only get tougher.

Mr. **FLEMING**. I expect so.

Chairman **HEINZ**. Very well.

Dr. Marshall and your associates, thank you very much.

This hearing is adjourned.

[At 1:40 p.m., the committee was adjourned.]

APPENDIX

MATERIAL RELATED TO HEARING

Item 1

ISSUES IN REUSE OF KIDNEY DIALYSIS DEVICES: IS REUSE ABUSE?

A Staff Report

Special Committee on Aging
United States Senate
John Heinz, Chairman

March 6, 1986

Stephen R. McConnell, Staff Director
Diane Lifsey, Minority Staff Director
Robin L. Kropf, Chief Clerk
Jim Michie, Chief Investigator
David H. Cunningham, Investigator

Staff Report

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ISSUES IN REUSE OF KIDNEY DIALYSIS DEVICES: IS REUSE ABUSE?

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ISSUES IN REUSE OF DISPOSABLE KIDNEY DIALYSIS DEVICES

A Staff Report of the Senate Special Committee on Aging.

United States Senate
John Heinz, Chairman

EXECUTIVE SUMMARY

INTRODUCTION.

This report summarizes the findings of a four month investigation by Committee staff. In the course of this investigation, interviews were conducted with scientists, clinicians and patients involved in hemodialysis study, practice and treatment. Staff also interviewed scores of managers and personnel in dialysis device manufacturing firms, standard-setting organizations, and in three federal agencies--the Food and Drug Administration (FDA), Health Care Financing Administration (HCFA) and the National Institutes of Health (NIH). Published research and information papers were reviewed as well as thousands of internal records from the three federal agencies.

WHAT IS DIALYSIS, AND HOW IS IT PRACTICED?

Dialysis is a critical life-sustaining treatment required to remove toxins, salt and water that accumulate in the blood of a person whose kidneys have ceased to function because of end-stage renal disease (ESRD).

Life-saving dialysis has been practiced for more than 20 years and today is provided by Medicare at a cost of over $1.5 billion dollars to more than 78,000 patients in over 1,200 dialysis clinics across the nation. Medicare funds 80% of dialysis costs.

A growing practice in dialysis clinics in recent years has been the reuse of certain dialysis devices that are labeled by manufacturers for "single use only". All dialysis clinics are reimbursed by Medicare at the same rate, regardless of whether they reuse disposables or not.

More than 60% of the dialysis clinics are reprocessing and reusing disposable dialysis devices as many as 20 and 30 times by flushing out and "disinfecting" them with a solution most often consisting of formaldehyde and water.

WHAT PROBLEMS ARE ASSOCIATED WITH REUSE?

PROBLEM #1: Tens of thousands of dialysis patients may be exposed to dangerous and unnecessary risks in the multiple reuse of disposable dialysis devices.

- o Formaldehyde, a potent toxin known to cause cancer and liver damage, is utilized by most reuse clinics to "disinfect" disposable dialysis devices.
- o Formaldehyde residue is trapped in the devices after reprocessing and leaches out into the blood of dialysis patients.
- o Dialysis patients are threatened with infection from deadly bacteria that may contaminate water supplies used in reprocessing disposable dialysis devices.
- o Dialysis patients complain of severe to minor formaldehyde reactions and overuse of blood thinning drugs to maximize the number of reuses of a dialysis device.

PROBLEM #2: Dialysis patients who submit to reuse often are not adequately informed of the risks, and many are denied freedom of choice on whether to reuse or not.

- o Dialysis patients often are intimidated and coerced into reusing their disposable dialysis devices.
- o Seldom are the potential risks of reuse provided to patients in writing so that the patient can make an informed decision on whether to reuse.
- o Seldom are patients given the freedom of choice on whether or not to reuse their disposable dialysis devices.

PROBLEM #3: There are no uniform and enforceable standards to ensure the safety and efficacy in the reprocessing and reuse of disposable dialysis devices.

- o FDA has failed to apply its good manufacturing practice (GMPs) regulations to reprocessors of disposable dialysis devices.
- o Lack of uniform standards for reuse has resulted in substantial variance in reprocessing techniques and procedures.
- o Both FDA and HCFA have taken a hands-off attitude toward reusing dialysis clinics by labeling it as a matter of "medical practice."

CAUSES OF THE PROBLEM.

CAUSE #1. Federal agencies have failed to do research necessary to assure the safety and efficacy of reuse.

> **Federal study of the safety and efficacy of reuse has been incomplete, has drawn questionable conclusions, and has failed to fulfill the mandate of Congress.**

> **The Health Care Financing Administration (HCFA) has failed to maintain an adequate ESRD data base to monitor the health outcomes of patients subjected to reuse.**

Cause #2: The Federal government has failed to ensure that dialysis patients' rights are respected.

Cause #3: FDA and HCFA have relinquished their responsibilities to ensure safety and efficacy and quality of care in dialysis.

> The FDA has substantially weakened its compliance policy in regulating reuse of disposable medical devices.

> FDA has failed to provide standards or guidelines for reuse of disposable dialysis devices.

> HCFA has failed to provide guidance and standards concerning reuse of disposable dialysis devices.

STAFF RECOMMENDATIONS.

Recommendation #1: Require DHHS to conduct the necessary studies, including randomized clinical trials on reuse of dialysis devices, (including dialyzers, blood tubing, transducer protectors and caps) to determine the safety and efficacy of this practice, as it is presently conducted.

Recommendation #2: The DHHS should withhold issuance of its proposal to establish lower composite rates for dialysis services (which assume reuse) until the safety and efficacy of reuse is determined.

Recommendation #3: If DHHS continues to allow individual physicians and clinics to decide whether or not to reuse, it should establish a two-tiered reimbursement system for dialysis facilities to reflect the difference in the cost between facilities that reuse devices and those that do not reuse. This will save money paid for excessive profits at reusing facilities, while it will avoid putting undue pressure to reuse on physicians and clinics that have decided reuse is unsafe or less effective.

Recommendation #4: DHHS regulations should be amended to include provisions that would require dialysis clinics to inform their patients in writing about potential risks associated with reuse and allow the patients the freedom to decide whether to reuse or not to reuse their disposable devices. Additionally, DHHS regulations regarding patients' rights and responsibilities should be amended to include provisions for requiring such informed consent and freedom of choice for patients.

Recommendation #5: The FDA should adopt uniform federal standards for the reuse of dialysis devices in accordance with the provisions of the Food, Drug and Cosmetic Act.

Recommendation #6: In accordance with and as provided in long standing law and regulation (21 CFR 820.3(k)), FDA should immediately impose FDA's Good Manufacturing Practices on all reprocessors of disposable dialysis devices.

ISSUES IN REUSE OF KIDNEY DIALYSIS DEVICES: IS REUSE ABUSE?

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INTRODUCTION.

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WHAT IS DIALYSIS, AND HOW IS IT PRACTICED?

Dialysis is a critical life-sustaining treatment required to remove toxins, salt and water that accumulate in the blood of a person whose kidneys have ceased to function because of end-stage renal disease (ESRD). The treatment requires the patient to be connected three times a week for four hours to a dialysis machine which filters out these life-threatening toxins. The only alternative to dialysis for treating ESRD is kidney transplantation. Medicare funds 80% of dialysis costs.

Life-saving dialysis has been practiced for more than 20 years and today is provided by Medicare at a cost of over $1.5 billion dollars to more than 78,000 patients in over 1,200 dialysis clinics across the nation. More than half (48,000) of the patients are 55 and older; over 26% (27,000) are 65 and older; and 34% of new patients annually are 65 and older.

A growing practice in dialysis clinics in recent years has been the reuse of certain dialysis devices that are labeled by manufacturers for "single use only" (please see examples of manufacturer labeling, and table depicting frequency of reuse in the U.S., pages 2-3). Reused most often are the plastic cylindrical dialyzer blood filter and the plastic blood lines through which the patient's blood flows to and from the dialyzer. Other equipment subjected to reuse includes the transducer filter and dialyzer caps.

50 EACH

18-813-001

TRANSDUCER PROTECTOR

Sterile, Nonpyrogenic
Do Not Contact With Alcohol
For Single Use Only
Caution: Federal Law (USA) Restricts This Device
To Sale By Or On The Order Of A Physician

LOT NO.

Sterilization Lot No.

COBE
Lakewood, CO 80215 USA

1 unit

CAT 03-9600-2
LOT M4C008

**Arterial
Blood Tubing Set**

For single use only

Sterile Non Pyrogenic Fluid Path if package is not damaged and protective sterility caps are in place.
See directions enclosed in carton prinr to use.

CAUTION: Federal (USA) Law restricts this device to sale by or on order of a physician.

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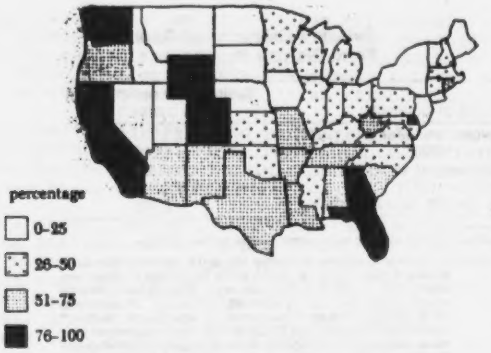

Geographical distribution of the frequency of dialyzer reuse as a percentage of patients treated by reprocessed hemodialyzers, 1984.

Source: The Association for the Advancement of Medical Instrumentation, November 1985.

Some dialysis clinicians believe that reuse of the dialyzer combats "first use syndrome", an allergic reaction to a new dialyzer. An estimated 99% of the reports on this "syndrome" have involved hollow fiber dialyzers, which are most often used in treatment today. An FDA analysis of data collected over a two year period showed that there are about 3.3 such reactions per 1000 patients. The FDA, however, discovered that in over 60% of the reported cases of first use syndrome, the dialysis facility failed to follow the manufacturer's instructions for preparing the dialyzer for patient use. Clinicians also have discovered that certain types of membranes used in dialyzers may cause allergic reaction, and switching the patient to another dialyzer with a different type of membrane solves the problem.

All dialysis clinics are reimbursed by Medicare at the same rate, regardless of whether they reuse disposables or not. Hospital-based clinics receive $131.00 per dialysis treatment, and non-hospital-based facilities, $127.00. A new disposable dialyzer costs about $10.00 and is the most expensive disposable device in dialysis. Blood lines cost about $3.00. Reprocessing of these two disposables saves about half to one-third the cost of buying new ones each time they are reused. Figures generated by the Office of Technology Assessment indicate that reuse of the dialyzers alone may result in excess profits of $80 million or more per year. (Please see Table, below.)

Selected Estimates of Savings From Dialyzer Reuse

Source of estimate	Savings per patient year[a] ($ current)
Fawcett and Mangles (1974) ..	$3,000
Foxen (1983)[b]	1,900
Hoffstein, et al. (1976)	1,600-2,400
Scribner (1977)...............	2,500-6,000
U.S. DHHS, HCFA (1981)[b]	2,000

[a] Rounded to nearest $100.
[b] Estimates are for dialyzer reuse without reuse of blood tubing.

SOURCES: B. Scribner, testimony at hearing before U.S. House of Representatives, Subcommittee on Health of the Committee on Ways and Means, Apr. 25 1977; P. A. Hoffstein, et al., "Dialysis Costs: Results of a Sample Study," *Kid. Int.* 9:286-293, 1976; and K. C. Fawcett and M. D. Mangles, "Reuse of the Gambro Lundia 17-Layer Dialyzer," *Dialysis and Transplantation* 3(1):38-40, 1974. Figures are derived from the summary in G. T. Willingmyre, *Reuse of Single-Use Hemodialyzers* (Washington, DC: Health Industry Manufacturers Association, 1979). Data from Fawcett and Mangles (above) and L. G. Foxen, "Is Reuse Cost Effective? A Case Study," in *Reuse of Disposables*, Association for the Advancement of Medical Instrumentation, Technology Assessment Report No. 6-83, Arlington, VA, 1983, were converted from cost savings per treatment by assuming 156 treatments per year. HCFA data are from U.S. Department of Health and Human Services, Health Care Financing Administration, Memorandum on Hemodialysis Reuse from Edward L. Kelly to Carolyne K. Davis, July 31, 1981.

Source: Office of Technology Assessment, December 1984, "The Hemodialysis Equipment and Disposables Industry"

When new, these disposable, or throw-away, devices are sterilized by manufacturers prior to shipping to dialysis clinics in accordance with the FDA's good manufacturing practices (GMP's). More than 60% of the dialysis clinics, however, are reprocessing and reusing these devices as many as 20 and 30 times by flushing out and "disinfecting" them with a solution most often consisting of formaldehyde and water. Although widespread, these "reprocessing" procedures are not regulated and checked under the FDA's GMP requirements for quality control.

WHAT PROBLEMS ARE ASSOCIATED WITH REUSE?

PROBLEM #1: Tens of thousands of dialysis patients may be exposed to dangerous and unnecessary risks in the multiple reuse of disposable dialysis devices.

More than 85% of the reuse clinics continue to reprocess and "disinfect" dialysis devices with formaldehyde, a potent toxin. Formaldehyde is known to cause cancer, liver damage and destruction of red blood cells. Research has shown that formaldehyde can cause the formation of antibodies in the blood that may encourage rejection of a kidney transplant. In addition, formaldehyde reportedly causes allergic reactions, central nervous system and menstrual and reproductive disorders. These adverse effects are enumerated and discussed in research papers that are listed in an attached bibliography.

Although there are other, and perhaps less toxic, disinfectants on the market, formaldehyde continues to be the germicide of choice for two reasons: (1) clinicians have used it for many years; and (2) it is inexpensive.

Study has shown, however, that formaldehyde residue is left behind in the dialyzer after "reprocessing", and that this residue leaches out into the patient's blood. Manufacturers indicate that repeated reuse of the blood lines causes spallation, or the breaking off, of small particles of plastic from the inner wall of the tubing and into the patient's blood. Acute and long term effects of the formaldehyde and the plastic particles on dialysis patients are not known; clinical studies needed to determine these effects have not been conducted.

The Centers for Disease Control recommends that a disinfectant solution containing at least 4% formaldehyde is needed to properly safeguard against bacterial contamination in reprocessing disposable dialysis devices. The toxic nature of formaldehyde, however, causes many clinics to use a disinfectant solution containing less than 4% formaldehyde. While these lower levels may lower the risk of adverse effects from formaldehyde, such practices increase the potential for bacterial contamination and infection in patients.

Patients who reuse their disposable dialysis devices face the risk of their devices being contaminated with virulent and life-threatening strains of bacteria. The CDC knows of at least several instances where the "reprocessing" water supplies in reuse clinics became contaminated with these deadly and infectuous non-tuberculous mycobacteria.

In one such tragedy several years ago, 27 patients in a dialysis center in Louisiana were infected with rapidly growing mycobacteria. The CDC reported that "one factor common to all patients was exposure to [re]processed dialyzers." The CDC hypothesized that "patients became infected when their blood circulated through [re]processed dialyzers that contained viable rapidly growing mycobacteria." According to the CDC, "between June 1982 and June 1983, 14 of the 27 patients *** died." The extent to which the bacterial contamination contributed to their deaths is unknown; an autopsy was performed on only one of the 14 patients who died.

CDC investigation revealed that the Louisiana dialysis clinic had been reprocessing their dialyzers with a 2% formaldehyde solution, which the CDC, in 1981 or earlier, had determined to be ineffective in killing off these virulent

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bacteria. In fact, the CDC had recommended in a June 1981 National Institutes of Health report that a 4% formaldehyde solution was needed to adequately protect against these deadly bacteria.

Moreover, a CDC survey last year of 115 dialysis clinics across the nation showed that "over 80% of these centers had mycobacteria in water associated with the clinic." A CDC scientist stated: These organisms cannot be ignored. How many outbreaks of non-tuberculous mycobacteria among dialysis patients are needed to indicate that 2% formaldehyde is an inadequate procedure for disinfecting hemodialyzers?"

Nonetheless, despite the longstanding CDC recommendation for a 4% formaldehyde solution, a full two-thirds of the reuse clinics continue to use less, some as little as 2% and even lower.

In 1983, the National Association of Patients on Hemodialysis and Transplantation (NAPHT) conducted a survey among its members concerning reuse of disposable dialysis devices. The Association for the Advancement of Medical Instrumentation (AAMI) Reuse Subcommittee analyzed some of the patient responses and found that "a majority of the responses reflected serious, negative experiences with reused devices." Results of the AAMI analysis were presented in table below in the Association's November 1985 report, "Hemodialyzer Reuse: Issues & Solutions."

Summary of 1983 NAPHT Responses on Reuse Experiences

- I. Negative Experiences (the majority fell into this category)
  - A. Formaldehyde reactions (ranging from severe to minor).
  - B. Over-heparinization. The report implied that this was done deliberately to improve the reuse characteristics of the device and to the detriment of the patient.
  - C. Non-disclosure of risks. Patients were evidently intimidated into signing releases.
  - D. Hostile, punishing staff. Patients who objected to reuse were allegedly punished.
- II. Positive Experiences (very few reported)
  - A. No first-use syndrome.
  - B. Full risk disclosure.
  - C. Sensitive, caring staff.

The AAMI report stated pointed that the NAPHT survey was not statistically valid and, therefore, "could be challenged as being the result of a 'biased sample'."

PROBLEM #2: Dialysis patients who submit to reuse often are not adequately informed of the risks, and many are denied freedom of choice on whether to reuse or not.

Under Medicare's existing reimbursement rates, it is still economically feasible for dialysis clinics to operate without reusing disposables, and 30% to 40% continue to do so, primarily for two reasons:

1. Many of the physicians in charge, the clinician-nephrologists, believe that there are too many unknowns associated with reuse, that it has yet to be proven safe and, therefore, choose not to include it in their medical practices;

2. Some of the non-reuse clinics have too few patients to make reprocessing and reuse of disposables cost-effective.

To date, however, there are no federal policies or guidelines on whether patients should be given freedom of choice on whether to reuse, nor on the exact nature of the information provided regarding potential risks of reuse.

Consequently, heated debate continues over whether patients who dialyze in reuse clinics should be advised of the potential risks and given freedom of choice on reuse.

All dialysis clinics, whether they reuse or not, require their patients to sign a "consent form" prior to beginning treatment. These consent forms vary in content and detail, but frequently provide only scant information on the risks and procedures in reprocessing and reusing disposable dialysis devices. A typical "consent form" might contain a single sentence referring to "multiple use" of dialyzers. The following are several examples:

> 1. ". . I understand that techniques for use of artificial kidneys including multiple use of artificial kidneys are employed for this treatment. .";
>
> 2. ". . The procedure of dialyzer reuse has been explained to me and I understand this process. ."; and
>
> 3. ". . The risks involved in reprocessing include exposure to the sterilant and not receiving one's own dialyzer. ."

The examples of "consent forms" collected during the Committee's investigation fail to mention any specific potential risks associated with formaldehyde exposure--cancer, liver damage, etc. Not even is the name of the "sterilant",formaldehyde, mentioned. Nor do any of the these forms inform the patient that their doses of the drug heperin, a blood thinner, may be increased to maximize the number of times the dialyzer can be reused (As the dialyzer is reused, blood clots are trapped in the filter fibers and increasingly reduce the efficiency of the dialyzer).

None of these "consent forms", except for one, provided the patient with freedom of choice on whether to reuse or not. The one exception, a form obtained from a clinic in Colorado,states: ". . I understand that if I refuse to allow the reprocessing of my dialyzer for multiple usage, my refusal will in no way affect my continued treatment in the hemodialysis program. ."

It is not uncommon for staff at some clinics to tell patients that, if they refuse to submit to reuse, they must find treatment elsewhere. There also have been cases where patients have been coerced and forced into submitting to reuse.

The State of California has drafted strict new regulations for its dialysis clinics concerning reprocessing and reuse of disposable dialysis devices. Mandated by the California Legislature, dialysis clinics in that state will be required to provide patients with a detailed "informed consent" statement similar to the example in Appendix 1.

PROBLEM #3: There are no uniform and enforceable standards to ensure the safety and efficacy in the reprocessing and reuse of disposable dialysis devices.

FDA, the federal agency charged with ensuring safety and efficacy of medical devices since 1976, enforces the "Good Manufacturing Practices" (GMP's). The GMP's are contained in the Code of Federal Regulations (21 C.F.R. 820) and require manufacturers to prepare and implement a "quality assurance program."

The GMP regulations specify procedures for manufacturing and reprocessing of devices: (a) written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design (21 C.F.R. 820.100); and (b) reprocessing procedures shall be established, implemented and controlled to assure that the reprocessed device meets original specifications (21 C.F.R. 820.115).

The FDA, however, has never applied these regulations to the more than 700 dialysis clinics who reprocess and reuse disposable dialysis devices. Instead, the FDA has taken the position that reprocessing and reuse of these devices is a matter of "medical practice"--not to be interfered with.

In a December 1, 1984 letter to the Kidney Patients Association, Dr. Edward Brandt, the then Assistant Secretary for Health, DHHS, stated: "this is not an area in which FDA or DHHS should properly be involved." A year later, in December

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1985, a HCFA official wrote the same patient organization: "the general question of reuse is a medical practice issue and one which should be decided by the patient's physician."

The consequence of the "hands-off" attitude of both the FDA and HCFA has led to widespread variance in reprocessing and reuse practices. Over the past decade, scores, perhaps hundreds, of different "recipes" for reprocessing disposable dialysis devices have been devised and used. Some nonspecific guidance on reprocessing has been published by such organizations as the National Kidney Foundation and the Association for the Advancement of Medical Instrumentation in an effort to bring some standardization to the procedure. These guidelines, however, provide extremely broad latitude to the practitioner and are far from matching up to the FDA's GMPs.

Although some of these "recipes" for reprocessing may be effective, there is no data base on which to make judgements since the FDA has yet to apply GMPs to the 700 or more reprocessors of disposable dialysis devices.

CAUSES OF THE PROBLEM.

Cause #1. Federal agencies have failed to do research necessary to assure the safety and efficacy of reuse.

Federal study of the safety and efficacy of reuse has been incomplete, has drawn questionable conclusions, and has failed to fulfill the mandate of Congress.

The Congress in 1978 mandated that the Secretary of the Department of Health and Human Services (DHHS) study the medical appropriateness and safety of cleaning and reusing dialysis filters by home dialysis patients. The law required a full report to be made to the Congress by October 1, 1979. A complete report has not been submitted to Congress.

In an attempt to meet the Congressional mandate, a coordinated plan for determining the medical appropriateness and safety of reuse was developed by the National Institutes of Health (NIH), Food and Drug Administration (FDA) and Center for Disease Control (CDC). The plan resulted in the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDKD), under the auspices of NIH, issuing a contract to study dialyzer reuse. The NIH study was to be conducted in three phases:

Phase I	Research of the published literature on reuse.
Phase II	In vitro testing of resterilization procedures to qualify resterilized dialyzers for human use.
Phase III	Clinical trials of resterilized dialyzers, to determine the health effects of reuse.

A contract for completion of Phase I and Phase II of the study on the "Multiple Use of Dialysis Devices" was awarded to the National Nephrology Foundation (NNF). NNF selected Arthur D. Little, Inc. (ADL) as its primary subcontractor to perform the actual research.

The critical third phase of the NIH study, however, was never begun. In a January 7, 1981 letter to HCFA, an NIH official asserted

> "... In some cases the fundamental research contribution [of these projects] to medical science would be fairly low. With this factor in mind, ... it would be relatively unlikely that NIH would fund some types of research that might have great interest to HCFA because of its economic impact....Clinical Trial of Multiple Use of Hemodialyzers ... [would have] a significant economic impact but a low contribution to basic medical science. Potential cooperation from HCFA: (a) Full funding of the needed clinical trials...."

This decision by NIH relegated the congressionally mandated report to "orphan" status, without an agency to fund or oversee its development during a critical phase. Concerned that the study was in jeopardy, the DHHS Inspector General's office wrote to NIH on January 15, 1981,

> "It has come to our attention that [NIH] had discontinued ... research into the efficacy and safety of kidney dialyzer reuse. Under the 1978 Amendments to the [Social Security Act], Congress mandated ... this research .... Now it appears unclear whether [NIH] or [HCFA] is primarily responsible for financing and administering the continuation of dialyzer research beyond Phase I .... Unless HCFA and NIH can ... resolve this issue, we plan to notify the Congress...."

The IG requested a "formal, written explanation which outlines your position on this issue", presumably to assist in the preparation of a report to Congress on HHS' progress in meeting the requirements of the 1978 amendments. The following responses were sent to the I.G.

o NIH: "...No funds were made available for dialyzer reuse studies, nor was responsibility assigned formally to any [Public Health Service (PHS)] Agency .... [HCFA and NIH] concur that since the issue about dialyzer reuse is one of SAFETY of dialyzer reuse, it would appear to belong more appropriately within FDA's sphere of responsibilities..."

o HCFA: "... The Department divided responsibility ... between HCFA and PHS.... PHS indicated that they expected to be reimbursed by HCFA for all research pertaining to their responsibilities under the legislation. HCFA responded to PHS that we expected PHS °to arrange for obtaining funds to conduct studies'.... PHS did not respond to this memorandum...."

o FDA: "... The FDA disagrees with [NIH's] statement that the responsibility for conducting dialyzer reuse research [belongs] within FDA's sphere of responsibilities.... The FDA position on reuse [is] ... When an institution or practitioner chooses to reuse a single-use [dialyzer] the responsibility for the safety and effectiveness of the reused device shifts from the manufacturer to the party responsible for the reuse.... A well-designed clinical study addressing the overall safety of reuse versus single-use might be desireable, however, such a study is not within the mission of the FDA...."

ADL released it's final report to NNF in February 1981, without any data from clinical trials. The final report on the study was released to NIH by NNF in June 1981.

The NIH (NNF) study has been cited repeatedly in numerous research documents and offical correspondence as authoritative evidence that reuse is safe. The report contains confusing and contradictory language, however, which suggests its findings are inconclusive and incomplete. For example, the key conclusion of the NIH report states that it resulted in the development of "protocol processes" (procedures) for "each component of the multiple use procedure". Further, the report contends that

> "[u]tilization of the specified procedures with suitable process and quality control will result in a reprocessed hollow fiber hemodialyzer equivalent in terms of function, cleanliness and sterility to a new hollow fiber hemodialyzer."

Of this finding, ADL later stated "[w]e believe that clinical studies are required to substantiate this conclusion."

Moreover, at the end of its chapter entitled "History of Clinical Experience" the NIH report draws a seemingly contradictory conclusion:

> "...clinical experience does not provide information which could appropriately lead to a standardized protocol for reprocessing dialyzers with suitable quality control and process control."

Later, at the end of a section describing the "History of Technical Experience", the NIH report further concludes

> "[t]he technical experience in the published reports does not provide a suitable data base for critical analysis of the parameters of importance for reprocessing of dialyzers. A definition of conditions to effect satisfactory rinsing, cleaning, sterilization and preparation for use of a reprocessed dialyzer is necessary."

In October 1981, when the principal subcontractor for the project, Arthur D. Little, Inc. (ADL), criticized the final report and NNF as misrepresenting their work. ADL, which had been responsible for conducting both the research on the literature and the _in vitro_ testing of dialyzers, wrote to NNF on October 9, 1981,

> "...[c]learly ... the interpretations and conclusions presented in the final report to [NIH] are those of the National Nephrology Foundation and not of Arthur D. Little, Inc....
>
> "... we urge that conclusions which could be applied to clinical practice, such as those relating to the concentration of formaldehyde used for sterilization, be substantiated where appropriate by clinical trials, as was envisaged in the original request for proposal for this assignment....

> "The final report omits most of the limitations which attended data and statistical statements in the ADL report, for those ADL-generated data and statements which were selected. In particular, the final report tacitly asserts that the dialyzers which NNF submitted to ADL for testing were sufficient in number and representation to permit conclusive statistical comparisons. The ADL report makes no such assertion, and in fact advises in several places that 'more extensive testing be performed to substantiate' its qualified findings."

In 1981, there was renewed interest at both HCFA and NIH in conducting clinical trials to determine the safety of reuse of disposable dialysis devices. A joint NIH/HCFA "ESRD Strategic Work Group" was formed and, on February 18, 1982, this body released its findings to the Secretary of HHS. The Work Group identified "four areas of critical importance", including the "initiation of clinical trials to determine the effects of hemodialyzer reuse". To date, no such clinical trials have been initiated.

The Health Care Financing Administration (HCFA) has failed to maintain an adequate ESRD data base to monitor the health outcomes of patients subjected to reuse.

In addition, the HCFA/NIH Work Group list of "critical areas" included a recommendation calling for

> "...a change in the focus of the Department's ESRD data strategy .... During the initial operating phase of the ESRD data system, several problems have impaired our ability to produce meaningful information. Some of the most critical weaknesses [include the fact that the] ... primary focus of the Medicare billing process is information needed for reimbursement - not medical statistics ..." [emphasis in original].

In December of 1982, however, the ESRD work group's recommendation was rejected and prevented from reaching the Secretary of HHS, because "... HCFA appears to have developed its recommendations in the subject issue paper without attention to their potential budgetary impact."

A successor work group, established by the Assistant Secretary for Health in February 1983 "to develop a coordinated response to the recommendations contained in the February 1982 Report ...", in October 1983 reaffirmed the need for significant improvements in the HCFA data base. This "PHS Coordinating Committee for End Stage Renal Disease" cited "the lack of systematic data on long-term morbidity or benefit in the reuse of dialysis of dialysis consumables" and called upon HCFA to "include information on dialyzer reuse" in its ESRD data base. The PHS Committee further asserted that such a data base was needed so studies can be initiated which would "compare the outcome of patients treated with dialyzers used once vs. multiple times."

In July 1985 nine experts representing providers, academia, NIH and HCFA met "to consider the establishment of a nationwide ESRD patient data system". In calling for a national ESRD patient registry, the participants noted

> "The history of the ESRD data system has been fraught with problems, both outside and inside HCFA. Despite the accumulation of large quantities of data by HCFA, it is only in the last two years, with the help of the ESRD Networks, and in particular during the last year with the aid of specifically interested HCFA staff, that reliable analyses, other than purely demographic information, have become available."

The ESRD Registry, the participants agreed, is needed

> "To provide appropriate selected national samples of patients to permit clinical studies leading to conclusions that may be generalized for national policy formulation."

In August 1985 a joint HCFA/NIH memorandum called for an initiative and issuance of a Request for Proposals entitled "Epidemiological Surveillance of ESRD Treatment in the United States". The objective of the proposed initiative was the establishment of a National ESRD Patients Registry, which would have as one of its goals assessment of "medical safety, efficacy, and the overall impact of current and newly developed interventions for the management of ESRD." The memorandum observes

> "... there is scant documentation on the comparative effectiveness of the various treatment modalities. There is only a limited amount of information currently available to physicians and health planners regarding medical (and fiscal) issues surrounding ESRD therapy. Therefore, a properly collected and analyzed data base must be generated to provide information to guide rational medical decisions.

Cause #2: The Federal government has failed to ensure that dialysis patients' rights are respected.

Federal law, enforced by the States under supervision from HCFA, requires that dialysis clinics which receive Medicare funds must observe certain fundamental patients' rights, including the following requirements found in the Medicare Conditions of Participation for ESRD providers:

> "The patient care plan is developed by a professional team and the patient.... The patient care plan is personalized

> for the individual, reflects the on-going psychological, social and functional needs of the patient."
>
> "All patients are fully informed of their rights and responsibilities...."
>
> "All patients are afforded the opportunity to participate in planning their medical treatment, and are transferred only for medical reasons, for the patient's welfare or that of other patients, or for nonpayment of fees (except as prohibited by the Medicare program). Patients are given advance notice to ensure orderly transfer or discharge."
>
> "Patients are treated with consideration, respect, and full recognition of their individuality and personal needs."
>
> "Patients are assisted in understanding and exercising their rights. There is an established grievance mechanism under which patients can participate without fear of reprisal."

Evidence and testimony gathered during the course of the Committee's investigation, summarized in Problem #2 above, suggests strongly that these guarantees are often little more than empty promises.

Cause #3: FDA and HCFA have relinquished their responsibilities to ensure safety, efficacy and quality of care in dialysis.

The FDA has substantially weakened its compliance policy in regulating reuse of disposable medical devices.

Prior to July 1981, FDA compliance policy regarding reuse of disposable medical devices was as follows:

> ". . [T]here is a lack of data to support the general reuse of disposable medical devices *** [T]he institution or practitioner who reuses *** should be able to, demonstrate: (1) that the device can be adequately cleaned and sterilized, (2) that the *** quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use.***FDA considers disposable devices which are being reused, and which have not been demonstrated to be capable of complying with the requirements in the above [sentence], to be adulterated***and in violation of 21 U.S.C. 331(k)."

On July 1, 1981, however, FDA published a new compliance policy guide which deleted the possible finding of "adulteration" prosecutable under 21 U.S.C. 331(k). That language was replaced with the following:

> ". . The reuse of disposable devices represents a practice which could affect both the safety and effectiveness of the device. Information developed regarding this practice should be referred to the [FDA's] Bureau of Medical Devices for review and evaluation."

Since 1981, the FDA has conducted only three field inspections relating to reuse of disposable dialysis devices. One of the cases involved a reported increase in patient deaths following a Texas clinic's decision to reuse blood lines. The informant was an employee of the clinic. An FDA inspection concluded that it could "not document any specific increase in deaths." The report further stated: "A review***reveals a cyclic expiration rate with increased numbers of deaths each fall and winter. We have not conducted any indepth statistical analysis, but [a] preliminary review of data [was performed]." Committee investigation determined that the FDA closed the investigation without interviewing the informant or any of his fellow workers.

FDA has failed to provide standards or guidelines for reuse of disposable dialysis devices.

Review of FDA documents indicates that the first mention at at that agency of the need for standards in reuse of disposable dialysis devices was in a June 1980 report, "Investigation of The Risks And Hazards Associated with Hemodialysis Devices." The report, which was prepared by an FDA contractor, advanced two goals: ". . to provide [FDA] with the information required for writing and implementing standards; [and] to provide *** additional data [for] evaluation of system component devices." The reported further stated:

> ". . The principal justification for reusing dialyzers is an economic one.*** [T]he practice of reuse is largely unregulated and therefore does constitute a potential threat to patient safety. *** The issue to be resolved *** is whether standards, either performance or disclosure, can be written for the reuse of dialyzers. At the present time, such standards cannot be proposed for two reasons: First, in the absence of definitive [clinical] studies, such as the one contemplated by the NIH, the necessary criteria to establish standards cannot be formulated. Second, at the present time, manufacturers label dialyzers *** for single use only. Unless these issues are resolved, standards related to reuse are not relevant."

However, as was discussed earlier in this report, the "definitive clinical studies" were dropped by NIH and have yet to be done. Further analysis of FDA, NIH and HCFA documents indicate that, by 1983, FDA apparently had given up on promulgating standards and shifted to discussion of "possibly develop[ing] guidelines on reuse procedures."

An FDA official's memo of July 6, 1983 stated: "Guidelines will *** provide assurance to patients *** that the government has studied the matter and has endorsed certain principles and/or procedures as adequate."

Later, in November 1983, the FDA decided to shift the responsibility for drafting guidelines away from itself to a nongovernmental group, the Association for the Advancement of Medical Instrumentation (AAMI). One month later, in December 1983, AAMI convened its Reuse Committee "to initiate work on a national consensus guideline for reuse of [dialyzers]".

To date, the 56-member AAMI committee, consisting of representatives of dialysis manufacturers, clinicians, patient organizations and federal agencies, has been unable to finalize its draft "Recommended Practice For Reuse Of Hemodialyzers." There continues to be controversy and disagreement over provisions for informed patient consent and various and sundry reprocessing issues. A vote by the membership on a 1985 draft of the AAMI "Recommended Practiced" produced 29 votes in favor, 3 opposed, 4 abstentions, and 20 not voting.

Representatives of both the FDA and CDC sit and vote on the AAMI Reuse Committee. Drafts of the AAMI "Recommended Practice" note, however, that "participation by federal agency representatives *** does not constitute endorsement by the federal government or any of its agencies."

HCFA has failed to provide guidance and standards concerning reuse of disposable dialysis devices.

HCFA has delayed formulation of policy and standards on reuse in anticipation of FDA formulating its policy based upon the AAMI Reuse Committee's final draft of its "Recommended Practice For Reuse of Hemodialyzers."

HCFA internal documents indicate that there has been discussion, beginning in July 1984, about the need for a an agency policy on reuse. A July 3, 1984 HCFA memo addressed "complaints from the [Washington] D.C. state survey agency concerning reuse of blood lines in a dialysis center." The HCFA memo stated:

> "[Centers for Disease Control] CDC does not have a reuse blood line policy *** We feel that the health and safety issues involving reuse of the dialyzer are similar in this situation. There should be a national policy disposition regarding the reuse of blood tubing in order to ensure the protection of the health and safety of patients."

A second internal HCFA memo in August 1984 concerned "Policy Guidance Regarding the Reuse of Disposables for Renal Dialysis." This memo addressed a suggestion for the "need for interim policy guidelines to address recent complaints about reuse of dialyzers and blood line tubing sets." The memo dismissed the need for an interim policy, stating: "[R]esults of [the AAMI study] are expected to be released in January 1985.*** We believe it is premature to consider any change in the regulations until the results of the [AAMI] project are evaluated."

HCFA received yet another complaint from the D.C. Government regarding the "need for clear guidelines from HCFA on reuse." A D.C. Government letter to HCFA stated:

> "[T]he federal ESRD regulations do not have clear guidelines on reuse [and] we are unable to enforce or persuade the [dialysis] facility to follow the standards of practice on reuse established by AAMI or the Kidney Foundation. Per the district's letter of September 12, 1984, once again clear direction from Region III [HCFA] is requested on the position of HCFA on reuse."

Again, in December 1985, HCFA responded to questions from the National Kidney Patients Association regarding policy on reuse:

> "The FDA is currently examining [AAMI's Proposed Recommended Practice for Reuse of Hemodialyzers]. When we receive the FDA comments, we will consider what steps, if any, should be taken by HCFA."

As was discussed earlier in this report, AAMI has yet to finalize its "Recommended Practice" and, therefore, there is continued in HCFA drafting standards and guidance concerning reuse of disposable dialysis devices.

STAFF RECOMMENDATIONS.

Recommendation #1: Require DHHS to conduct the necessary preclinical and clinical studies to determine whether the reuse of disposable dialysis devices is safe and efficacious.

Recommendation #2: The DHHS should withhold issuance of its proposal to establish lower composite rates for dialysis services (which assume reuse) until the safety and efficacy of reuse is determined.

Recommendation #3: If DHHS continues to allow individual physicians and clinics to decide whether or not to reuse, it should establish a two-tiered reimbursement system for dialysis facilities to reflect the difference in cost between facilities that reuse devices and those that do not reuse. Such a system would allow Medicare to reduce payments to reusing facilities, but would not create undue pressure to reuse at clinics where

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physicians have decided reuse is unsafe or inappropriate for patients.

Recommendation #4: DHHS regulations should be amended to include provisions that would require dialysis clinics to inform their patients in writing about potential risks associated with reuse and allow the patients the freedom to decide whether to reuse or not reuse their disposable devices. Additionally, DHHS regulations regarding patient rights and responsibilities should be amended to include provisions for requiring such informed consent and freedom of choice for patients.

Recommendation #5: The FDA should adopt uniform federal standards for the reprocessing and reuse of disposable dialysis devices in accordance with the provisions of the Food, Drug and Cosmetic Act.

Recommendation #6: In accordance with and as provided in long standing law and regulations (21 CFR 820.3(k)), FDA should immediately impose FDA's Good Manufacturing Practices on all reprocessors of disposable dialysis devices.

APPENDIX 1.

Draft Informed Consent Statement from the State of California.

75209. Informed Consent Text for Hemodialyzer Reuse.

The following text shall be used by the dialysis facility in any consent form used for the purpose of securing patient consent for the reuse of hemodialysis filters:

My name is (patient's name) and I am a dialysis patient at (name of dialysis facility), a dialysis facility which practices dialyzer reuse. (Name of person who has explained the reuse procedures) has explained to me the procedures for the reprocessing of dialyzers at this facility. I understand that if I consent to dialyzer reuse, my dialyzer will be reprocessed prior to use on me each time.

It has been explained to me that if I consent to reuse, a specific dialyzer will be assigned only for my use and that the dialyzer may be used to treat me as many as (number of maximum dialysis treatments) times before being replaced with a new dialyzer. I understand that the manufacturers of dialyzers do not recommend their reuse. However, there is a long histroy of reuse of dialyzers. Some people who have studied reuse document adverse effects and others indicate reuse is a safe and effective practice.

I understand that if this dialysis facility reprocesses my dialyzer according to the reprocessing procedures available for my review at this unit, the disadvantages associated with or claimed for reuse are:

(a) Entry of formaldehyde, a chemical used to disinfect dialyzers, into my blood system. The long-term effects of at the levels which may enter my body are unknown.

(b) Increased possibility of infection and/or fever producing reactions.

Further, the advantages associated with or claimed for reuse are:

(a) Lower incidence of back and chest pain, cramps, fever, sweating, blood pressure problems, nausea and vomiting often associated with the initial use of a new dialyzer.

(b) Reduced cost to the renal dialysis program at this dialysis facility which may or may not result in added patient service benefits or will result in the following patient service benefits: (space for additional factors to be added by the dialysis facility).

I understand that I have the right not to participate in the dialyzer reuse program at this dialysis facility for any reason whatsoever. I also understand that I will not lose my rights or priveleges now or in the future if I decide not to participate. I am aware that I have certain rights as a participant in reuse, and these rights include:

(a) The right to ask questions at any time about dialysis reuse and reprocessing procedures, and the right to receive from the supervising practioner and/or his/her assistant answers which fully, fairly, and understandably respond to such questions.

(b) The right to withdraw my authorization for dialysis reuse by oral request, followed by a written notice, to the supervising practitioner for any reason, and that I do not have to explain why to anyone. I further understand that none of my rights or privileges related or unrelated to dialysis will be negatively affected or denied.

(c) The right to a copy of this consent form after I sign it and that the original will be kept with my medical record.

(d) The right to file a written complaint with the dialysis facility and the Department of Health Services Licensing and Certification Division, and expect a resolution of that complaint by the dialysis facility.

(e) The right to expect safe and effective reprocessing of my dialyzer.

(f) The right to know the number of times my dialyzer has been reprocessed prior to my dialysis treatment.

I have read this consent form and I do hereby AGREE to the reuse of dialyzers during the course of my treatment at this dialysis facility.

__________________ (Signature of patient or guardian or conservator and Date)

I have read this consent form and I do hereby NOT AGREE to the reuse of dialyzers during the course of my treatment at this facility.

__________________ (Signature of patient or guardian or conservator and Date)

NOTE: Authority cited: Sections 208(a), 417.10, 1225, and 1275, Health and Safety Code.

Reference: Sections 417.10 - 417.15, 1226, and 1276, Health and Safety Code.

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Item 2

19

Formaldehyde in Dialysis Patients

A Review

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Exposure to formaldehyde is associated with a variety of effects in dialysis patients, including sensitization, eosinophilia, and chromosomal damage. Most notably formaldehyde stimulates antigenic changes in erythrocytes that cause the development of antibodies. With new and reused filters, residual formaldehyde left after sterilization is leached from the filter during dialysis and enters the patient. As formaldehyde contacts the erythrocytes, it apparently forms an active hapten that stimulates the production of antiformaldehyde and anti-N-like antibodies. Anti-N-like antibodies may develop in more than 30% of the patients who are exposed to formaldehyde during dialysis. Antibodies related to formaldehyde exposure have been associated with hemolysis, anemia, and changes in the hematocrit. In a few patients who had received renal transplants, erythrocyte agglutination, caused by the antigen–antibody reactions, probably blocked microcirculation in the kidney and caused its rejection by the host. Perhaps by understanding the ways that patients are exposed to and affected by formaldehyde during dialysis, systems for dialysis and patient protection may be improved. This information may also help elucidate formaldehyde's potential to elicit reactions in healthy people when the exposure occurs by other routes.

THE PROPENSITY OF FORMALDEHYDE (HCHO) to cause irritation, sensitization, cancer, and mutations following dermal or respiratory contact has received much attention (*1–5*). By contrast, the potential of HCHO to cause organ changes or effects by other routes of exposure has received little attention (*6*). Since 1972, information has been developed about the effects of HCHO in patients who receive dialysis therapy (*7*). This therapy may result in exposure to HCHO by intraperitoneal and intravenous injection. Although personnel who administer dialysis therapy, as well as the patients themselves, may touch or breath HCHO (*8*, *9*), this chapter focuses on the

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effects in patients following the injection of it during dialysis. Perhaps by reviewing studies of these patients, new insights may be gained into HCHO toxicity and ways to improve dialysis therapy.

W. Kolff developed the first artificial kidney for human use in 1943; it was successfully used in 1945 (*10*). During the 1950s and 1960s, dialysis as a therapeutic procedure was conducted on a limited scale. In 1961, development of the Teflon shunt for repeated circulatory access (hollow fiber artificial kidney) permitted therapeutic dialysis of patients with renal failure to become more common. By 1970, dialysis was generally available for commercial use (*11*). Since 1970, although hemodialysis therapy has been simplified and extensively applied, the hollow fiber dialyzer has remained commonly employed. In December 1982, 65,765 patients received regular dialysis therapy in the United States at an annual cost of more than $1.6 billion or approximately $25,000 per year per patient (*12*, *13*). By assuming that the incidence of new patients in the United States is similar to that of Australia, some 7000 people each year may start on dialysis therapy for the first time (*14*).

In the United States, patients either self-administer therapy at home or receive it in one of the 1218 service or health centers (*13*, *15*). In both situations, the therapy is expensive. Because it is expensive, health centers and patients search for ways to reduce the costs of dialysis (*11*, *12*, *16*). One common way to save money is by reusing dialyzers. Although reuse of dialysis filters started before 1964 (*12*), it is becoming more common because of economic pressure (*17*). For example, in 1978 and 1979, approximately 15% of the patients reused dialyzers; in the fall of 1981, 27.5% reused them; and current estimates are that 50% of patients now reuse filters (*18*). Because a new dialysis filter may cost up to $30 and recycling a filter costs $4–10 (*18*), reuse has the potential to save significant sums. The more times a filter can be reused, the more money is saved (*19*). Some filters have been successfully reused for 3 years (*12*). To further illustrate this point, one health center with 45 regular hemodialysis patients saved approximately $85,000 annually or $2000 per patient per year (*14*). Others report similar savings (*16*). Most patients receive treatments three times per week. Therefore, if the number of new filters purchased was reduced by 50% (*14*, *16*), and if each patient saved $25 per treatment, potential savings for the United States alone might exceed $250 million per year. If the cost of new filters decreases, savings from reuse may also decrease.

Sterilization

Whether a dialysis filter is new or reused it must be sterile. Without proper maintenance of sterility, infectors (bacteria and virons) might be introduced directly into the patient. Methods for sterilizing dialyzers that have been tried include the use of cold storage; γ-radiation (*20*); proteolytic enzymes (*11*); and solutions of benzalkonium chloride (*21*), ethylene oxide

(22), hydrogen peroxide (*11*), hypochlorite, and formalin or formaldehyde (23, *24*). Of these, HCHO was recommended as the sterilant with several advantages in 1965 (*21*). It remains widely used today (*25*). The current trend is to use sterilizing solutions having concentrations of 2.0–4.0% HCHO. However, concentrations of up to 12% formaldehyde (30% formalin) have been used (*21*, *26*, *27*).

New and used dialyzers contain materials that operate as "chemical sinks." These may collect formaldehyde during sterilization and storage and release it during use (25). The commonly used hollow fiber dialyzer illustrates this point. During its fabrication the cellulosic fibers interact chemically with the polyurethane potting material and partially inhibit the hardening or curing of the polyurethane. The situation causes a thin film or cuff of polymethane gel to form around each fiber (25). During storage, HCHO diffuses into the gel film (25); during use, it leaches out and enters the patient. Although polymethane gel appears to be the primary chemical sink, dialyzers contain others, such as gaskets, potting material, tubing, and fibers (*24*, *25*). HCHO may enter a patient from nondialyzer sources in the dialysis system as well. For example, in one hospital a water filter containing cotton fibers bonded with melamine–HCHO resin was inserted between the water tap and the dialyzer. In this instance, HCHO from the resin in the water filter leached through the dialyzer into the patients (28).

Exposure Concentrations

Easy, accurate, and reliable methods for measuring low concentrations of HCHO in blood or in dialyzer compartments have not been generally available (*23*, *29*). Consequently, exposure concentrations that have been reported in the literature were either obtained in laboratory experiments and then used to predict exposure during dialysis or represented less accurate measurements at bedside of residual HCHO in dialyzers prior to use. Primarily because of its convenience, the clinitest has been commonly used at bedside to measure residual HCHO in dialyzers to which patients would be exposed (*30*). Its use did little to protect patients from exposure to formaldehyde because the lowest concentration that it can accurately measure may exceed 50 ppm (*29*, *31*).

By using methods other than the clinitest, detection of HCHO at the concentration of 5.0 μg/mL (5 ppm) is done in some health clinics (*16*). These methods are not generally available to patients who dialyze at home. Methods for routinely and accurately measuring HCHO concentrations of 1.0 ppm at bedside have recently been developed and should gain wider use soon (*32*).

Many factors affect the amount and concentration of HCHO to which a patient is exposed during dialysis. These include the type of filter used and the number and frequency of dialysis treatments. These three factors depend in part on the patient's needs and availability of service resources.

However, additional factors include the concentration of formalin that is used to sterilize and store the equipment, the extent to which HCHO is rinsed from the equipment prior to use, and the length of time that flow through the dialyzer is stopped between rinsing and use, or during use itself (*15*, *23–25*). Although these additional factors may be controlled, proper rinsing of equipment requires consideration of more than just removing the excess HCHO or sterilant.

If the sterilant is removed over too long a period of time or if inadequate concentrations of sterilant are used, potentially harmful infectors may grow in the filter or equipment (*15*, *27*). If the rinse is inadequate and too little HCHO is removed, the residual amount may be sufficient to cause toxicity.

To rinse all HCHO from the sinks within a dialyzer is extremely difficult. Lewis et al. (*24*) flushed a dialyzer with saline for 3 h and found that even after the procedure HCHO was leached from it. Shaldon et al. (*33*) found that 100 L of H_2O failed to rinse all ^{14}C-formaldehyde from a dialyzer that had been sterilized with it by a standard method that they used to prepare dialyzers for patients. In addition to the difficulties in rinsing HCHO from the dialyzer, the time that patients will devote to rinsing it is limited. Lewis et al. (*15*) suggest that a patient should not be expected to spend more than 1 h rinsing a dialyzer before each use.

If flow through the dialyzer stops, the concentration of HCHO that is available to the patient increases. This result occurs because HCHO from the sink equilibrates in time with that in the blood and dialysate compartments. The extent of the increase depends partially on how long the flow is stopped. When flow is restarted, a bolus of HCHO enters the patient in the first few hundred milliliters. In this situation, exposure concentrations reach easily 40 ppm (*24*). Koch et al. (*34*) studied the HCHO concentration in the effluent of Kiil dialyzers at the start of 220 dialyses during home use. They found the concentration ranged from 0.3 to 108 mg/dL (mean = 6.7 mg/dL). This finding means that some patients were infused with more than 100 ppm of HCHO. Lewis et al. (*24*) estimated that even after a complete rinsing process, 13 mg of HCHO was leached from a hollow fiber dialyzer during a routine cycle of use.

Newer rinsing procedures and sensitive convenient methods to measure HCHO have helped reduce most exposure concentrations to the range of 2.0–5.0 ppm (25). Perhaps more sensitive detection methods and better construction of dialyzers can reduce this exposure to HCHO even more in the future.

Effects of Exposure

For many patients, exposure to low concentrations of HCHO during dialysis has not caused any observable effects. Indeed, hemodialysis was once used to maintain blood pH levels by removing excess formic acid from a 58-

year-old man who drank 8 oz of formalin in a suicide attempt (*35*); it probably saved his life. For other patients, exposure to HCHO has been associated with a variety of toxic effects. These include a burning sensation at the site of injection (*24*), possible cytogenetic damage (*36*, *37*), inhibition of ATP production by erythrocytes (RBC) (*28*), development of anti-N-like (ANL) and antiformaldehyde (anti-F) antibodies (*38*, *39*), hemolysis of RBC, decrease in the life of RBC (T ½), and changes in the hematocrit (*40*). In a few patients, the exposure to HCHO was associated with eosinophilia, hypersensitivity, possible anaphylactoid reactions (*41*, *42*) or formalin reactions (*12*) and, at high concentrations even death (*43*).

Physicians with experience in dialysis report that hepatomegaly and/or persistently high concentrations of liver-related enzymes develop in the sera of some patients (*32*, *44*, *45*). These changes in seemingly healthy dialysis patients may be due to several factors including, in part, a direct or indirect effect of formaldehyde on the liver (*6*).

Chromosomal damage in dialysis patients has been related by Goh and Cestero (*36*, *37*) to exposure to HCHO. These workers examined 1187 metaphase specimens of cells that they took directly from the bone marrow of 40 dialysis patients. Preparations obtained from relatives of the patients served as controls. They found a "marked" increase in chromosomal abnormalities including aneuploides, breaks, and structural changes in dialysis patients. Measurements made during a mock sterilization of a dialyzer in the laboratory indicated that patients had received 126.75 ± 50.84 mg of HCHO during each treatment (*36*, *37*). Because their studies did not include groups of similar dialysis patients without exposure to HCHO, more research is needed to understand the possible relationship between HCHO and chromosomal damage in dialysis patients.

The effects of HCHO on RBC probably occur through at least two processes: (1) changes in their metabolism and (2) changes in their immunogenic potential. Orringer and Mattern (*28*) associated the installation of a water filter between a tap water outlet and several dialyzers with an outbreak of hemolytic anemia among hemodialysis patients. Because the water filter's construction included melamine-formaldehyde resin, they investigated the effects of HCHO on RBC metabolism. They exposed RBC to HCHO for 5 min and then incubated them in vitro for 2 h with inosine as the only substrate. Pretreatment of RBC with HCHO inhibited glycolysis by reducing nadide (NAD) to NADH and thereby caused a 90% reduction in cellular adenosine triphosphate (ATP) concentrations during the 2-h incubation. Exposure to as little as 0.1 mM HCHO was able to reduce glycolysis and ATP content in RBC. When pyruvate was also present, a HCHO-related decline in ATP did not occur. The maximum effective amount of HCHO was 1.0 mM. According to Orringer and Mattern, this amount was only one-tenth of the concentration of HCHO that was in 1 L of fluid that they obtained from a dialyzer filter. These workers also showed that, using the same systems, melamine did not affect RBC metabolism.

Belzer et al. (*46*) described a medical case involving a man in whom RBC "cold" agglutinins caused localized infarcts and rejection of a transplanted kidney. The patient had received dialysis therapy for a year before the renal transplant was attempted. The antibodies that caused the infarcts reacted with N-positive RBC. The next year Howell and Perkins (*7*) described for the first time the development of ANL antibodies in patients who received chronic hemodialysis. They contrasted the incidence of 12 in 416 patients who had ANL antibodies with an extremely rare occurrence of anti-N antibodies per se in healthy people. Several researchers have subsequently confirmed the frequent presence of ANL antibodies in dialysis patients (*29, 38, 39, 47–49*).

Workers also subsequently substantiated the work of Belzer et al. (*46*). For example, Gorst et al. (*50*) related formaldehyde-induced ANL antibodies to renal graft failure.

Howell and Perkins (*7*) listed several potential causes for ANL antibody production and included exposure to HCHO as one possibility. Although they did not specifically establish HCHO as the cause, they eliminated pregnancy and prior transfusions as possible stimuli for ANL formation. Crosson et al. (*49*) eliminated other chemicals, bovine implant materials, prior serum transfusions, and bacterial and viral infections as stimuli for ANL antibody production. Ultimately several workers showed that HCHO alone stimulated the production of ANL antibodies (Table I) (*33, 48, 49*).

Table I. Anti-N-Like Antibodies in Dialysis Patients Exposed to Formaldehyde

No. Studied	*No. with Anti-N-Like Antibodies*	*Percent*	*Reference*
416	12	3	7
40	6	15	48
430	38	9	49
288	37	13	33
111	18	16	51
117	42	36	34
239	14	6	75
22	6[a]	27	39
71[b]	3[c]	16	38
82	15	18	15
196	60	31	29

[a] Twenty patients (91%) showed a separate antiformaldehyde antibody.

[b] Nineteen patients were exposed during resterilization with HCHO.

[c] Seventeen patients (89%) showed a separate antiformaldehyde antibody.

Howell and Perkins (*7*) speculated correctly that the incidence of 12 in 416 underestimated the proportion of patients who would develop ANL antibodies. Subsequent studies report a 12–24% incidence of ANL antibodies in patients who were dialyzed at health centers (*48, 51, 52*). Moreover, the incidence of patients dialyzed at home is generally greater than that of patients in dialysis centers and may reach nearly 50% (*15, 53*). Lynen et al. (*54*) showed that the incidence of patients with formaldehyde-dependent antibodies increased with time on dialysis therapy, and that all patients who had been treated for 5 years or longer had the antibodies. Table II shows the incidence of anti-N antibodies in people with normal renal function. In one study, only 8 of 45,000 people had auto-anti-N antibodies (*55*). Other researchers project that approximately 0.3% of a normal population would possess auto-anti-N antibodies (*33*).

ANL antibodies are producible by patients having MM, MN, or NN antigenic RBC (*7, 48*). The order of the potential for agglutination with ANL is NN > MN > MM (*54*). Because ANL antibodies react with N antigen and because MM-type RBC also react with ANL, HCHO seems to be capable of altering M antigens to become N-like. Also, it seems as if either N or N-like antigens may stimulate ANL production.

Little is known about the characteristics of ANL antibodies. Kaehny et al. (*51*) suggested that inactivation of ANL antibodies by 2-mercaptoethanol suggests that they may be of the immunoglobulin M (IgM) class. More recently, Lynen et al. (*54*) found that the antibodies that agglutinate native NN cells are exclusively of the IgM fraction of immunoglobulins, whereas antibodies directed against formaldehyde-altered NN red cells are mainly immunoglobulin G (IgG) in addition to IgM. Depending upon the titer, the ANL antibodies will agglutinate RBC at temperatures ranging from 4 to 37 °C (*49, 56, 57*). Some have found that the optimal reaction temperature range for the agglutination of ANL with RBC is between 12 and 18 °C (*57*). However, recent studies demonstrate a considerable amount of warmer antibodies (IgG) that could react at body temperature in dialysis

Table II. Incidence of Auto-Anti-N Antibodies in People Who Did Not Receive Dialysis Therapy

Cases Examined	*No. with Anti-N*	*Percent*	*Reference*
45,000	8	0.0178	55
50	0	0	33
71	0	0	38
74	0	0	29
1366[a]	19	1.39	74

[a] People with abnormal antibodies.

patients (*54*). Although ANL antibodies are probably not species specific, they may be specific for RBC (*47*).

In one study, only 6 of the 22 patients who were exposed to HCHO developed anti-N-like activity, but 20 of the 22 specifically agglutinated HCHO-treated RBC. Thus, the agglutination of HCHO-treated RBC did not depend only on the formation of ANL (*39*). This result raised the possibility that another factor was involved in a progression of immunogenic changes in RBC. Sandler et al. (*38*) named this new agglutinating factor antiformaldehyde antibody (anti-F). To these workers anti-F seemed to be a high-titer IgG immunoglobulin that reacted with formaldehyde-treated RBC independently of whether they were of the MM, MN, or NN phenotype (*38*). In 1981, Sharon et al. found that the removal of ANL antibodies by absorption onto RBC antigens with ONN did not affect the activity of anti-F (*47*).

The mechanism by which HCHO causes ANL antibodies to form involves a multi-step process and the MN antigen system on the RBC membrane (*7, 54, 58*). Lynen et al. (*54*) described a three-stage time-related process for the development of formaldehyde-dependent antibodies. The stages were defined according to the agglutination of different cell types by the patient's sera. In Stage I, the patients own RBC agglutinated only after pretreatment with HCHO, and the reaction had no relation to the MN system. In Stage II, NN RBC also agglutinated if they had been pretreated with HCHO. In Stage III, agglutination of native NN RBC also occurred (*54*). Undoubtedly, HCHO reacts with the N antigens on the RBC surface and probably also reacts at other sites on the RBC (*38*). In 1981, Sharon speculated that formaldehyde might exert an effect by neutralizing a negative charge on the RBC membrane. Because HCHO induces ANL antibodies in MM-type patients, it apparently has the ability to convert the antigenicity of MM on the RBC membrane (*29*). RBC M and N antigens behave as simple codominant alleles at a single locus (*59*). An important difference between the two antigens is the existence of a terminal sialic acid on the M antigen, but not on the N one. Recent studies show that in healthy people, HCHO reacts with the terminal sialic acid moiety on the RBC M antigen and thereby converts it to an N-like antigen (*60*). Perhaps the sialic acid is the source of negative charge on the RBC membrane that becomes neutralized, as Sharon (*47*) speculated.

The fact that HCHO-N RBC are agglutinated by anti-N antibodies in dialysis patients but not in healthy people indicates that differences in the N and N-like antigens are found (*61*). The HCHO-modified N and/or M antigens apparently stimulate the production of or develop in association with anti-F, an IgG antibody (*47*). The production of anti-F apparently precedes production of ANL antibodies by approximately 6 months (*47*). This finding means that during the process of immunization, a shift in production from IgM- to IgG-type antibodies occurs (*51*); Lynen et al. (*54*) suggest that this shift may occur by their Stage II. Anti-F appear to cross-react with the N-antigen on the RBC membranes (*39, 47*). The cross-reaction develops slowly, but leads to a type of "spreading sensitivity." Larger titers of anti-F seem to yield a greater extent of cross-reactions. Anti-N antibodies may also cross-react with the M antigen sites on the RBC (*62*). The extent to which this cross-reaction between M antigen and ANL antibodies occurs is not known.

The in vitro incubation of sera with HCHO not only stimulates the production of specific antibodies but also reduces the activity of other antibodies. Specifically, a 1-h incubation of sera with a 1.0% solution of HCHO at a dilution of 1 : 1 (sera to HCHO) reduced the titers of anti-A and anti-B isoagglutinins (*47*). In this study, 110 of 200 sera samples showed a HCHO-induced decrease in selected antibodies (*47*). The effect was generally more pronounced in sera with inherently low antibody titers, although the response depended in part on the specific antibody that was agglutinated. This effect of HCHO may already be important in some patients because antibodies may play a role in inhibiting infections and promoting healing. Even without exposure to HCHO, these health-promoting events may be less than desirable in patients with renal failure.

In 1975, Cestero et al. (*42*) reported that anaphylactoid-type reactions occurred in two otherwise stable dialysis patients. These reactions included nasal congestion, rhinorrhea, conjunctival injection, circumoral paresthesias, pallar, dyspnea, laryngeal constriction, and marked hypotension that was unresponsive to volume replacement. Both patients had marked eosinophilia, and both had been dialyzed chronically with hollow fiber filters that were originally sterilized at the factory and, later, between uses with formaldehyde. The reactions did not occur when the same patients were dialyzed on two different coil filters that eliminated exposure to formaldehyde (*42*). These researchers related the eosinophilia and reactions to repeated exposure to formaldehyde. In 1979, Hoy and Cestero (*41*) again reported that anaphylactoid-type reactions that were related to formaldehyde occurred in two patients. These were the same two patients who were in the earlier report by Cestero et al. (*42, 45*). Nevertheless, in one patient, the anaphylactoid reactions did not develop until the man had received dialysis therapy for 3 years. Then the reactions became progressively more marked with time, as did his eosinophilia. This patient has subsequently developed severe reactions on dialyzers that were not sterilized with formaldehyde (*45*).

Hakim et al. (*63*) reported that two patients suffered cardiovascular collapse within 2 min after the start of dialysis. They related the occurrence of chest pain, dyspnea, and hypotension in certain dialysis patients to new cuprophane-membrane dialyzers and complement activation (*63*). Hakim et al. (*64*) found that the reuse of filters decreased the capacity of the cuprophane membrane to activate complement, but did not alter the capacity of cellulose acetate membranes to activate complement. Thus, complement activation in their studies did not increase, as does the formation of ANL antibodies, with repeated reuse of dialysis filters.

Charytan et al. (65) reported that allergic-type reactions occurred in 5% of dialysis patients without eosinophilia, but in 22% of the patients with it. Hoy and Cestero (*41*) found that 20 of 37 patients who used hollow fiber filters and formaldehyde resterilization had eosinophilia. In contrast, none of the nine patients who used coil filters and were therefore unexposed to formaldehyde had eosinophilia. These workers later documented a 38% incidence of eosinophilia in a group of dialysis patients who were exposed to formaldehyde. This incidence was significantly greater than that in either a group of azotemic patients or in a group of control patients who were not exposed to HCHO (*41*). The incidence of eosinophilia in HCHO-exposed patients increased with time. Several potential causes were found for eosinophilia in chronic dialysis patients including exposure to ethylene oxide, plasticizers, poly(vinyl chloride), and various drugs (*22*, *41*). But, for some patients, exposure to formaldehyde seems to be the cause (*41*).

Discussion

Some of the effects in dialysis patients that occur after their exposure to formaldehyde seem similar to those that occur after exposure to it by other routes. For example, separate reports in 1982 by Spear (*66*) and by Suskov and Sazonova (*67*) associate the exposure of humans to formaldehyde by inhalation with increased incidences of cytogenetic abnormalities. Formaldehyde is also mutagenic to human cells that are cultured in vitro (*68*). These data are consistent with the findings by Goh and Cestero (*36*, *37*) of an unusually high incidence of chromosomal abnormalities in patients who were exposed during dialysis to formaldehyde. Together these data support the proposition that formaldehyde may be mutagenic in humans under certain circumstances.

Several reports discuss the development of dermal and respiratory sensitization reactions upon exposure to formaldehyde or related products (*3*, *69*). A recent report (*69*) suggests that dermal sensitization reactions to formaldehyde are Type I allergic reactions. Based on such reports, one might predict that sensitization reactions would develop in people whose blood is exposed to formaldehyde. The studies of dialysis patients substantiate the development of such immunologically based changes. The agglutination of ANL antibodies with RBC evidences a Type II allergic reaction, and the anaphylactic changes suggest Type I allergic reactions (*69*). It would be interesting to know whether or not immune responses involving ANL antibodies, anti-F antibodies, or eosinophilia might also develop after chronic exposure to formaldehyde by inhalation.

The chronic exposure of rats and mice to 5.6 and 2.0 ppm of formaldehyde by inhalation is associated with nasal carcinoma, metaplasia, or adenomas (*70, 71*). Although detailed mechanisms of the development of nasal cancer have not been described, formaldehyde initiates and promotes certain carcinogenesis processes in vitro (*72, 73*). Many dialysis patients have been chronically exposed to formaldehyde in concentrations exceeding 5.6 ppm. These data raise the possibility that exposure to formaldehyde places dialysis patients at an increased risk of developing cancer. Additional research is needed to help define the nature and extent of that risk as well as the risks associated with its mutagenic potential.

Exposure to formaldehyde by inhalation has been associated with systemic changes in laboratory animals and humans; these include changes in the reproductive and central nervous systems and various organs (*2, 3, 4, 6*). Some untoward changes that seem to occur without apparent cause in dialysis patients could be related to their exposure to formaldehyde. One example of such changes is the unexplained hepatomegaly and/or elevated concentrations of liver enzymes in the sera of dialysis patients. Additional research could help elucidate formaldehyde's role, if any, in such change.

Perhaps the development and widespread use of accurate and sensitive methods of measuring residual formaldehyde in dialyzers will help answer some of these questions and provide safer therapy for dialysis patients. Other questions may be answered only by additional research.

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Item 3

FORMALDEHYDE AND HEPATOTOXICITY: A REVIEW

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Exposure to formaldehyde appears to be associated with hepatoxicity in many species, including humans, following injection, ingestion, or inhalation. Macroscopic, microscopic, and biochemical manifestations in the liver include alterations in weight, centrilobular vacuolization, focal cellular necrosis, and increased alkaline phosphatase concentrations. Time-related changes in the pattern of the effects are suggested as one goes from acute exposure by inhalation at greater concentrations to repeated exposure at lesser concentrations. Although the hepatic changes are generally not extensive and can be reversible following acute exposure, the potential exists for them to progressively become more serious with repeated exposures.

There are several possible mechanisms for the toxicity. Depending on the route of exposure, these could include direct effects on hepatocytes and/or indirect effects through the circulatory and immune systems. The catabolism of formaldehyde includes conversion to CO_2 *by reactions involving glutathione. Many hepatotoxic chemicals require glutathione for detoxification. Formaldehyde may then have the potential to cause additive toxicity with such chemicals in some circumstances.*

INTRODUCTION

Before 1979, concern about formaldehyde (HCHO) toxicity generally focused on its ability to cause irritation and sensitization (U.S. Dept. of Health, Education and Welfare, NIOSH, 1976a, 1976b; Public Health Service, 1945; National Research Council, 1981). On October 8, 1979, the Chemical Industry Institute of Toxicology (CIIT) announced the preliminary results of their chronic toxicity study, which showed that HCHO causes nasal cancer in rats (Chemical Industry Institute of Toxicology, 1979). After that, attention focused more on understanding the carcinogenic and mutagenic properties of HCHO. Several groups of scientists subsequently reviewed

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these properties (Federal Panel on Formaldehyde, 1980; IARC Monographs, 1982; Ulsamer et al., 1984; Swenberg et al., 1980).

In contrast to the extensive attention paid to the carcinogenic effects of HCHO, little attention has been paid to its potential to cause organotrophic effects on the liver and kidneys, as well as the circulatory, hematopoietic, and nervous systems (Skog, 1950; Battelle Columbus Laboratory, 1981; National Research Council, 1980; IARC Monographs, 1982; Lynen et al., 1983). In recent years, a few instances have been reported that involve people who developed hepatitis while being exposed to HCHO (Palmero, 1982; Associated Press, 1982; U.S. District Court, 1983). To understand these and other reports, information is needed about the relationship between exposure to HCHO and liver changes. In this review article, we attempt to summarize the available information and to draw attention to some of the reported biological consequences of exposure to HCHO which have passed largely unnoticed. In so doing, creative research in this area of toxicology may be stimulated.

HEPATIC EFFECTS IN ANIMALS

Historical Studies

Between 1897 and 1914, several scientists studied the acute toxicity of HCHO in a variety of species (Bower, 1909; Fischer, 1905; Harrington, 1898; Iwanoff, 1911; McGuigan, 1914). Before 1900, at least two scientists had reported on the hepatotoxicity of HCHO. In 1898, Hansen injected 1.5 ml of 0.5–4% formalin into the gall bladder of cats and produced changes in the liver ranging from cloudy swelling to total necrosis. In all cases slight inflammatory changes and evidence of hepatic regeneration were found (Fischer, 1905). Harrington (1898) studied the disinfecting potential of HCHO gas. He exposed two rabbits to HCHO gas from 4–6 ml of a 40% solution of formalin, which he vaporized during 2 overnight attempts to disinfect a room. One rabbit was found dead on the second morning; the other was found dead 36 h later. Harrington said that the liver of the first rabbit "Shows marked injection, with granular and fatty degeneration of cells around the veins of lobules." Of the second rabbit, he wrote, "In the liver there is considerable dilatation of hepatic veins, with some degeneration of liver cells in the center of the lobules" (Harrington, 1898). Harrington also found epithelial degeneration in the bronchioles and renal degeneration and congestion.

Fischer (1905) probably conducted the first systematic studies of the hepatotoxicity of HCHO. He used a 10% solution of formalin and paraformaldehyde as the sources of HCHO for gavage or injection and for inhalation, respectively. His research included the acute exposure of rats, guinea pigs, cats, rabbits, and dogs by inhalation, oral gavage, and injection (pulmonary, subcutaneous, intramuscular, extraocular, and intraperitoneal). The acute inhalation studies in guinea pigs and rats were accomplished by volatilizing 3–6 g paraformaldehyde with a Schering lamp in a room of

5.5 m^3 over exposure periods of 1.5 h (3 g) to 6 h (6 g). The air exchange rate in the room was not reported.

He found that acute exposure to HCHO caused inflammation and cloudy swelling in the liver; this was associated with vacuolated protoplasm, destruction of nuclei, and focal hepatic necrosis, especially after inhalation. Fischer exposed two rabbits, one guinea pig, and one dog to multiple, intraperitoneal injections of dilute (1 : 1000 or 1 : 2000) formalin for periods of time ranging from 4 d to 38 d. He periodically adjusted the dose volume and concentration to elicit toxicity but preserve life. These animals developed cloudy swelling and focal necrosis in the liver. In the dog, the liver also had marked fatty degeneration. Fischer's studies also revealed toxic effects on the respiratory system, eyes, muscles, and kidneys following exposure to HCHO by various routes of administration.

Fischer's research was followed by that of McGuigan (1914), who described hyperemic changes in the liver and kidneys following the injection of HCHO into dogs. McGuigan suggested that, because some investigators did not find hyperemic changes after acute exposure to toxic levels, the interval between the end of exposure and death might be critical if such effects were to become evident. This may be the first suggestion that time may influence the nature of hepatic change that appears after exposure to HCHO.

Modern Studies

Forty-five years after Fischer's report, Skog (1950) studied the acute lethality of HCHO. He administered 0.15-0.46 g HCHO/kg subcutaneously (sc) to mice and 0.30-0.64 g/kg sc or 0.6-1.7 mg/l (about 500-1400 ppm) by inhalation to rats. Skog found the LD50 (over a 3-w period) to be about 300 mg/kg in mice (sc), and 420 mg/kg (sc) and about 1 mg/l (830 ppm) by inhalation in rats (based on a 30 min exposure to the vapors of a 35.5% solution of HCHO). Following injection, most animals died within 24 h; following inhalation, 18 of 49 rats died within 24 h. The oral and the subcutaneous administration, as well as the inhalation, of HCHO caused macroscopic and microscopic alterations in the livers of all animals (Skog, 1950). The sc administration of HCHO caused microscopic hyperemia in the liver, while the inhalation of HCHO caused hyperemia, perivascular edema, and necrosis of the liver. Skog also found that these toxic levels caused bronchitis, slight hyperemia, edema, and hemorrhages in the lungs and hyperemia and edema in the kidneys. These changes were similar to those reported by Harrington (1898) and by Fischer (1905).

Salem and Cullumbine (1960) found that the liver enlarges in mice, guinea pigs, and rabbits after a single 10-h exposure by inhalation to 16 ppm (19 mg/m^3) of HCHO. These workers also reported edematous, hemorrhagic lungs and ruptured alveolar septa in animals inhaling HCHO. Similarly, Murphy et al. (1964) found an increase in liver weight and in the liver-to-body-weight ratio in rats that were exposed for 18 h to 35 ppm HCHO vapor. The increase in liver weight following acute exposure to HCHO in high concentrations may be accompanied by inflammation and hyperemia (McGuigan, 1914; Fischer, 1905; Skog, 1950).

These historical and more recent studies demonstrate that acute exposure to HCHO in sufficiently large amounts (16 ppm and more) is associated with systemic organ toxicity. They also raise a question as to whether hepatic changes would occur after exposure to lesser amounts of HCHO for longer periods of time.

One abstract was found that indicates that HCHO applied on the skin of mice caused "considerable liver damage," but no hepatomas (Searle, 1968). The concentration of HCHO in the solution, the number of applications, and the length of the study were not specified; a full report was not published. (In Searle's study, hepatomas were produced by dermal applications of 4-chloroquinoline-*N*-oxide and 4-nitropyridine-*N*-oxide.) Additional research is necessary before the significance of Searle's study will be clear.

Several studies showed that subchronic inhalation of 3.0 ppm and less of HCHO caused liver changes. Gofmekler (1968) placed groups of 12 female albino rats each in inhalation chambers and exposed them either to air, or to 0.83 or 0.01 ppm HCHO. Exposures lasted 22 h/d for about 6 wk (10–15 d before mating, 6–10 d during the mating period, and during pregnancy). The author did not state how the exposure concentrations were determined.

Formaldehyde caused systemic effects in both the dams and their offspring. Pregnant rats that inhaled HCHO had 14–15% longer gestation periods, compared to those of the control dams. The total body weight and the weight of the adrenal glands of offspring from dams exposed to 0.01 or 0.83 ppm were greater than those of the control offspring. At 0.83 ppm, the kidneys and the thymus of offspring from dams exposed to HCHO weighed more than those from the control offspring. These changes probably reflect the growth of the offspring, which naturally occurs during a longer gestation. In contrast, exposure to 0.01 or 0.83 ppm HCHO decreased the lung and the liver weights of the offspring. These dose-related changes cannot be explained by a long gestation.

In 1969, Gofmekler and Bonashevskaya summarized the results of Gofmekler's earlier experiments (1968) with HCHO on embryonic development in rats and emphasized the histopathological data. They found that the liver cells of offspring from dams exposed to 0.83 ppm HCHO had large nuclei, more numerous and enlarged extramedullary hematopoietic centers, and finely granulated RNA (as revealed by methyl green). Depletion of glycogen in peripheral parts of lobules, numerous segmented forms in the sinusoids, and a mild hypertrophy of Kupffer's cells were also noted (Gofmekler and Bonashevskaya, 1969).

Inhalation of small concentrations of HCHO affects the liver in male rats. Fel'dman and Bonashevskaya (1971) exposed 4 groups of 25 male albino rats each continuously for 3 mo to atmospheric concentrations of HCHO of 0.0012, 0.035, 1.0, and 3.0 mg/m^3 (0.001, 0.03, 0.83, or 2.45

ppm) in dynamic-flow exposure chambers. The authors did not state how the exposure concentrations were determined. A fifth group of 25 rats served as the controls. The lungs of rats exposed to 0.83 or 2.45 ppm HCHO had microscopically visible moderate hyperemia and proliferated lymphohistocytic elements in the interalveolar walls and in the peribronchial and perivascular spaces. By microscopic examination, the livers of rats in these two groups had nuclear polymorphism, a profusion of binuclear cells around the triads, focal hyperplasia, and activation of the elements of the reticuloendothelial system. Liver cells had moderately decreased glycogen content and coarsened and less dense RNA granules. They did not report any of these liver changes in rats exposed to concentrations less than 0.83 ppm, or in the control rats. These authors also reported mild changes in the kidneys, adrenals, and cerebral cortex of rats exposed to 0.83 or 2.45 ppm HCHO (Fel'dman and Bonashevskaya, 1971).

Biodynamics, Inc., exposed rats, hamsters, and monkeys to concentrations of 0.2, 1.0, or 3.0 ppm HCHO for 22 h a day, 7 d/wk for 26 wk. The study was conducted in two phases, which were separated in time by about 6 mo (Biodynamics, Inc., 1980; Formaldehyde Institute, 1982). In phase I, animals were exposed to 0.2 or 1.0 ppm HCHO. In phase II, animals were exposed to 3.0 ppm only. Both phases had control groups for each species and sex. The tissues in phase I were examined 6 mo before those in phase II (J. Clary, 1982, personal communication). At 3.0 ppm, both the liver weight and the liver-to-body-weight ratio were significantly decreased in rats. Focal hepatic necrosis was reported for 4 of the 5 rats whose livers were examined in the 1.0-ppm group. However, it was not seen in rats in whose livers were examined microscopically in the control and other treatment groups (Formaldehyde Institute, 1982). The significance of this and other sporadic liver changes that were reported to have occurred in the 1.0-ppm group is unclear.

In 1978, Battelle Columbus Laboratory, under contract with the Chemical Industry Institute of Toxicology, initiated a carcinogenic study of HCHO (CIIT study). This inhalation study involved 240 rats and 240 mice (120 per sex) in each of 3 dose groups (2.0, 5.6, and 14.1 ppm HCHO) and a control group (for each species). It included gross, morphological, histological, and biochemical analyses of major organ systems at preset times over a 30-mo period (Battelle Columbus Laboratory, 1981). The CIIT generously provided us with a complete set of data on all animals.

The CIIT data reveal many changes in the liver (Table 1). As part of this review, we used a Fisher exact test (one-tailed) to statistically compare the incidence of livers having one or more pathological change(s) in control mice and in mice exposed to 14.1 ppm HCHO. Our analysis was limited to mice (both sexes) that had been killed for examination at 6, 12, 18, and 24 mo. In the control group, 37 of 108 (40%) mice had at least one liver change, and in the 14.1-ppm group, 55 of 104 (53%) mice had at least one change; the difference between the groups is significant ($p < 0.005$). Because this super-

TABLE 1. Summary of Changes in Liver in the CIIT Study Following Exposure by Inhalation to Formaldehyde

Species	Exposure	Time	Change	Direction of change vs. concurrent controls	Comment
Mice					
Females	5.6 ppm	24 mo	Absolute liver weight	Decreased ($p < 0.05$)	Possibly a random event
Females	14.1 ppm	6 mo	Relative liver weight	Decreased ($P < 0.05$)	Measured in relation to body weight
Females	14.1 ppm	18 mo	Histologic appearance	For 12/19: hepatocellular, centrilobular, cytoplasmic vacuolar degeneration. For For 9/19: had multifocal areas of hepatocellular degeneration with necrosis.	Significantly different from the incidence in the concurrent control group, 0/20 ($p < 0.0001$)
Males	14.1 ppm	6 mo	Histologic changes	For 6/10: had centrilobular cytoplasmic vacuolization.	Significantly different from concurrent control group, 0/10 ($p < 0.005$)
Rats[a]					
Females	14.1 ppm	18 mo	Histologic changes	Increased	Hepatic clear cell foci
Females	14.1 ppm	0–24 mo	Grossly visible hepatic masses		Necropsies after unscheduled deaths
Males	14.1 ppm	12 mo	Liver weight	Decreased ($p < 0.05$)	
Males	14.1 ppm	12 mo	Relative liver weight	Decreased ($p < 0.05$)	Measured in relation to body weight
Males	14.1 ppm	18 mo	Liver weight	Decreased ($p < 0.05$)	
Males	14.1 ppm	24 mo	Liver weight	Decreased ($p < 0.05$)	
Males	2.0 ppm	0–24 mo	Mottled appearance		Grossly visible changes at necropsy after unscheduled deaths
Males	5.6 ppm	0–24 mo	Mottled appearance		Grossly visible changes at necropsy after unscheduled deaths
Males	14.1 ppm	0–24 mo	Mottled appearance		Grossly visible changes at necropsy after unscheduled deaths

[a] Many of the rats showed nasal cancer and various other upper respiratory effects. These changes obscure the significance of these liver alterations, which could have been secondary to the other somatic effects.

ficial analysis reveals nothing about the nature of the difference, the groups were examined further for patterns of change. For purposes of these analyses, we assumed that the pathological evaluations applied the same criteria to all animals in all groups.

Much of the difference in incidence of mice with liver changes between the control and 14.1-ppm groups could be accounted for by the development of centrilobular cytoplasmic vacuolization, hepatocellular degeneration, and necrosis after 6 mo of exposure to HCHO. At 6 mo only, 6 of 10 male mice exposed to 14.1 ppm HCHO had centrilobular cytoplasmic vacuolization. According to CIIT scientists, this lesion was characterized histomorphologically by small intracytoplasmic vacuoles with indistinct borders. There was an occasional hepatocyte with an enlarged nucleus in the centrilobular area. These lesions were not present in the 10 control males. Our comparison revealed a significant difference in the incidence of this lesion between males in the control group and those in the 14.1-ppm group ($p < 0.005$).

At 18 mo, 12 of 19 female mice that were necropsied in the 14.1-ppm group had livers with centrilobular cytoplasmic vacuolar degeneration. Because male mice were not killed at 18 mo, their tissues were not available for microscopic examination. The alteration in the females tended to involve all the lobules. Cells were characterized by small vacuoles that filled the cytoplasm. The vacuoles were surrounded by a thin, delicate, eosinophilic-staining membrane. Swenberg (1980b) described these changes as compound related "central lobular fatty degeneration" and "hepatocellular degeneration." The final report states that 9 of these 12 females also had multifocal areas of hepatocellular necrosis. It also states that necrotic hepatocytes were randomly distributed and were associated with acute inflammatory response. These lesions did not occur at that time in mice from the other groups, including the controls (Battelle Columbus Laboratory, 1981). The differences in incidence between females in the control and the treatment groups (12/19 versus 0/20) is statistically significant ($p < 0.0001$). These liver changes are reminiscent of those reported by Fischer (1905) and by Gofmekler and Bonoshevskaya (1969).

At several times during the CIIT study, livers of mice and rats exposed to HCHO weighed significantly ($p < 0.05$) less than those from the respective control groups (Table 1). The report states that in male rats at 12 mo the "decrease in absolute kidney and liver weights, may be the result of exposure to 14.1 ppm of HCHO" (Battelle Columbus Laboratory, 1981).

Macroscopically visible hepatic changes occurred in more rats that were exposed to HCHO and died before 24 mo than they did in controls which died in the same period. Hepatic masses were seen at necropsy in 8 of 67 female and in 8 of 57 male rats that were exposed at 14.1 ppm HCHO. Hepatic masses were not reported to have occurred in the control rats that died before 24 mo. Mottled architectural patterns of the liver developed in 5 of 16 female rats at 2 ppm, 7 of 19 females at 5.6 ppm, 7 of 67 females at 14.1 ppm, and 4 of 57 male rats at 14.1 ppm. This macroscopic alteration occurred in 1 of 19 control rats that died during the same period (Battelle Columbus Laboratory, 1981). Although gross and microscopic changes in the livers were seen in both species in the study, the concentrations of serum enzymes (SGOT, SGPT, LDH) in the animals varied greatly and showed no consistent patterns of change and few differences among the groups. Many of the rats in the CIIT study developed extensive nasal cancer (Swenberg et al., 1980a). Because of this, it is difficult to relate liver changes in these animals directly to HCHO per se. Interestingly, the Biodynamics study also noted that the livers of some rats which were exposed to 0.2 or 1.0 ppm HCHO had a mottled discolored appearance at necropsy. The change developed in 7/40 rats (0.2 ppm) and 5/40 rats (1.0 ppm). Discolored livers were not seen in the 40 concurrent control rats (Formaldehyde Institute, 1982).

In other studies, exposure to HCHO at toxic concentrations elicited only minimal changes in the liver. Rats and mice were exposed to HCHO by inhalation at 4.0 or 12.7 ppm for 6 h/d, 5 d/wk, for 13 wk (Battelle Columbus Laboratory, 1979). A control group was also maintained for 13 wk. A third group was exposed to 38.6 ppm HCHO, but it had to be terminated after 9 exposures because the toxicity was excessive. Microscopic examination of the tissues revealed several lesions that resulted from nine 6-h exposures to 38.6 ppm HCHO. In rats, these included ulceration and necrosis of the nasal turbinates and trachea, pulmonary congestion and hemorrhage, and congestion of the hepatic sinusoids.

After 13 wk the liver weights were significantly increased in female mice exposed to 12.7 ppm. When corrected for body weights, the liver weight to body weight ratios were significantly reduced in the male and female mice exposed to 4.0 ppm HCHO.

Battelle Northwest Laboratories (1981) reported the results of a study in mice exposed to lethal amounts of HCHO by inhalation. Six groups of 10 male and 10 female mice were exposed 6 h/d, 5 d/wk, for 13 wk (65 exposures) to concentrations of either 0, 2, 4, 10, 20, or 40 ppm HCHO. There was a significant depression of weight in both sexes at 20 ppm and an 80% mortality rate at 40 ppm. Although the toxicity was marked, the only hepatic effects were a decrease in the liver-to-body-weight ratio (females only) and focal necrosis in two mice, at 40 ppm (Battelle Northwest Laboratories, 1981).

As one might expect, the macroscopic and microscopic changes that occur in the liver after exposure to HCHO are associated with biochemical changes as well. Murphy et al. (1964) exposed 8 male rats to air containing 35 ppm of HCHO for 18 h; 8 control rats received clean air only. Twenty-four hours after the start of exposure, the livers were subjected to macroscopic examination and biochemical analysis. The livers of rats exposed to HCHO had significantly greater alkaline phosphatase activity than did those of the controls (Murphy et al., 1964). These workers found that other irritating chemicals, including acrolein, NO_2, and SO_2 also increased alkaline phosphatase activity in the liver of rats. Although the authors did not measure alkaline phosphatase or glucocorticoid concentrations in the serum, they suggested that the changes in the alkaline phosphatase in the liver resulted from a reaction to stress (Murphy et al., 1964).

In addition to changes in alkaline phosphatase, other biochemical changes have been reported to occur in the livers of animals exposed to HCHO. Sanotskii et al. (1976) exposed pregnant and nonpregnant rats to 6 mg/m^3 (5 ppm) HCHO for 4 h/d for 20 d. They used the Quick-Pytel test to evaluate liver function. This test is based on the ability of the liver to synthesize glycine and to conjugate it with benzoic acid to form hippuric acid. In nonpregnant rats, but not in pregnant ones, exposure to HCHO decreased the urinary excretion of hippuric acid from 143 mg/d to 106 mg/d ($p < 0.05$), following administration of sodium benzoate. The authors interpreted this as indicating that the effect of HCHO on liver function is greater in nonpregnant animals than in pregnant ones (Sanotskii et al., 1976). The reasons for this apparent difference in toxicity to pregnant rats is unknown, but may relate to an increased capacity in them to metabolize formaldehyde. Nagornyi et al. (1979) reported that exposure to 0.5 mg/m^3 (0.4 ppm) HCHO for 2 mo decreased hippuric acid excretion by 24% in rats. The abstract available to us contained few details.

In two reports, Gofmekler and colleagues (Gofmekler et al., 1968; Pushkina et al., 1968) presented the results of biochemical analyses of the livers of pregnant rats and their offspring after exposure (described above) to 0.83 or 0.01 ppm HCHO. They found a statistically significant, dose-related decrease in the concentration of DNA (and ascorbic acid) in the livers of dams and offspring. Based on this, they concluded that exposure to HCHO reduces the synthesis of hepatic nucleic acids in the rat. A decrease in O_2 consumption by liver tissue has been reported to occur in some rats that were exposed to 0.03 ppm HCHO for 4/d for 7 d (Nikiforov et al., 1980).

POTENTIAL MECHANISMS

Since HCHO is a highly reactive, water-soluble chemical, HCHO gas is absorbed primarily in the upper respiratory tract (Egle, 1972; Swenberg, 1980a). However, HCHO could migrate to remote tissues and affect them by direct and indirect mechanisms. When absorbed to particulates, HCHO reaches the lower respiratory tract (Amdur, 1959, 1960). Formaldehyde that contacts body tissues reacts with amino acids (Hemminki, 1981; Tyjihak and Rusznak, 1980), proteins (Feldman, 1973; Siomin et al., 1973), nucleotides (Hemminki, 1981), and nucleic acids (Feldman, 1973; Chaw et al., 1980). The reaction of HCHO with small molecules such as amino acids and nucleotides produces labile conjugates. These may carry HCHO to tissues that are remote from the respiratory tract. It is possible that the changes in various organs, such as the liver, kidney, and hemopoietic tissues, that develop after HCHO is inhaled reflect such a process. However, a recent study indicates that the formaldehyde concentration in the plasma of rats is not altered immediately after a 6-h exposure to 15 ppm HCHO (Heck and Casanova-Schmitz, 1983). This finding does not rule out the possibility of a bonding of HCHO to carrier compounds that are not detected by the method, or of transient increases in HCHO concentrations.

Formaldehyde may also cause effects in remote tissues by indirect mechanisms, such as depletion of available glutathione (GSH). Liver and other tissues rapidly metabolize HCHO following a reaction with GSH (Uotila and Koivusalo, 1974a, 1974b) or tetrahydrofolic acid (THFA) (Blakley, 1960; Kallen and Jencks, 1966). The reaction with GSH is particularly important because many drugs and other chemicals require GSH for detoxification (Chasseaud, 1979).

Exposure of isolated rat hepatocytes to HCHO, or to substances that produce HCHO by oxidative demethylation (ethylmorphone, benzphetamine, or aminopyrine), causes a 26–85% reduction in cellular GSH (Jones et al., 1978). Formaldehyde alone, when added at concentrations of 0.2-1 m*M* to the incubation medium, reduced GSH in the hepatocytes by 20–50%. Neither methanol (10 m*M*) nor formic acid (2 m*M*) had any effect on GSH levels when added to the incubation medium. A similar decrease in GSH occurs *in vivo* in guinea pigs when they are exposed to 10 ppm HCHO for 4 h/d, 5 d/wk, for 13 wk and sacrificed 3 d after the final exposure (Mecler, 1978). Under these conditions, GHS concentrations decreased in the liver and kidney by 26 and 10% respectively, while lung GSH increased by 38%. Inhalation of 10 ppm NO_2 in the same study did not affect liver GSH levels.

Concentrations of GSH in liver can also be depleted by exposure to a variety of drugs and chemicals. For example, GSH decreases by 22% in the liver of mice 2 h after the ingestion of ethanol (4.1 g/kg); similar effects occur in rats and in baboons after chronic ingestion of alcohol (Videla and Valenzuela, 1982). These authors suggest that ethanol-induced liver damage may be related to the stimulation of liver lipid peroxidation coupled with decreased levels of liver GSH.

Exposure to atmospheric pollutants such as diesel engine exhaust (DEE) can also decrease the concentration of GSH in the liver (Chandhari and Dutta, 1982). Thus, a subchronic (8 wk) exposure to rats to 6 mg DEE/m^3 decreased the concentration of hepatic GSH by approximately 14%, whereas exposure to DEE for 2 or 4 wk did not decrease it. The authors suggested that the decrease in GSH concentration may be related to the presence of polycyclic aromatic hydrocarbons in DEE. The possible role of HCHO (which is also in DEE) was not examined.

Drugs such as phenacetin and thiophene or solvents such as trichloroethylene, 1,1-dichloroethylene, and methylchloride also lower liver GSH (Videla and Valenzuela, 1982; Dodd et al., 1982).

Ku and Billings (1982) showed that the toxicity of HCHO to isolated hepatocytes *in vitro* increases when liver GSH is depleted by diethylmelamine. Other chemicals and drugs that increase their hepatotoxicity by depleting GSH include acetaminophen, aniline, aspirin, bromobenzene, furans, vinylchloride, aromatic hydrocarbons, and styrene (Plummer et al., 1981; Benedetti et al., 1975; Buttar et al., 1977; Kaplowitz et al., 1980).

Species vary in their responsiveness to GSH-depleting agents. For example, Vainio and Mäkinen (1977) tested rats, guinea pigs, mice, and hamsters for their response to GSH-depleting chemicals. Rats and guinea pigs were most responsive to the GSH-depleting effects of acrylonitrile (administered ip) whereas mice were most responsive to styrene (administered ip). Davis et al. (1974) studied the effects of acetaminophen on the liver of guinea pigs, rabbits, rats, mice, and hamsters following an ip injection of 150-1500 mg/kg. Hamsters and mice were the most susceptible to the hepatotoxic effects of this drug. The severity of the damage (centrilobular necrosis) was positively related to the depletion of liver GSH. At 300 mg acetaminophen/kg, mice and hamsters had an 80% decrease in liver GSH; guinea pigs and rabbits had a 30% decrease, and rats had a 10% decrease. People may be more susceptible than are rats to chemicals that deplete liver GSH, since they have only about one-eighth the concentration of liver GSH that rats have (Lauterberg et al., 1982).

In humans, acetaminophen also decreases GSH levels in the liver by as much as 50% and causes hepatotoxicity. Lambert and Thorgevisson (1976) used bromosulfophthalein (BSP) excretion to measure liver function; they found that acetaminophen in high doses increased the retention of BSP in humans by 16.8%. Therapeutic doses of acetaminophen increased BSP retention by 2-10%.

Plummer et al. (1981) proposed that the depletion of GSH to less than 30% of the normal concentration in liver increases the toxicity of many chemials by altering detoxification mechanisms and allowing the amount of electrophilic metabolites to increase. It is not clear whether smaller reductions in GSH will exert a similar effect.

As shown above, exposure to many drugs, chemicals, and pollutants, including HCHO, can affect GSH levels in the liver. Exposure to any one of these GSH-requiring chemicals could, therefore, increase the toxicity of another such chemical. Together they could produce liver damage at levels at which either alone may be ineffective. These include some drugs (such as acetominophen) that may be taken to relieve symptoms of HCHO toxicity. For many of these substances the lower effective doses are unknown.

Theoretically, HCHO need not necessarily reach the liver to cause hepatotoxicity. Oxyphenisatin, halothane, and other chemicals can cause autoimmune types of reactions that may lead to chronic hepatitis (Zimmerman, 1978). Formaldehyde has been used as a sterilant in some hemodialyzers (Gorst et al., 1977). Consequently, patients using these dialyzers have been exposed directly to HCHO and as a result have developed RBC antigens that cause strong reactions with anti-*N*-like antibodies in them

(Boettcher et al., 1976; Fassbinder et al., 1976; Gorst et al., 1977). Recent work (Lynen et al., 1983) shows that the dialysis patients also have elevated levels of IgG and that there are stages of formaldehyde-dependent RBC immunization in humans. The data also show that dialyzed patients apparently develop autoantibodies from their exposure to HCHO (Lynen et al., 1983). The literature confirms that dermal (and probably pulmonary) sensitization reactions develop in experimental animals and in humans exposed repeatedly to HCHO (U.S. Dept. of Health, Education andWelfare, 1976a; 1976b; Ulsamer et al., 1984). In highly sensitive individuals, small amounts of HCHO may initiate adverse reactions (National Research Council, 1980; Slater, 1981). Since HCHO reacts readily with amino acids, protein, nucleic acids, and nucleoproteins, it might cause immunological-based hepatotoxicity by several possible mechanisms or stages (Zakin and Boyer, 1982; Lynen et al., 1983). For example, it could form HCHO-protein haptens, or it could cause rearrangement of the protein structure itself. If HCHO reacted with an organ-specific protein, the result might be a localized reaction to that organ. Any of these reactions might lead to possible immunological-based or an autoimmunological-type hepatotoxic reaction, such as those caused by oxyphenisatin, halothane, and other chemicals in susceptible individuals (Zimmerman, 1978; Zakin and Boyer, 1982). If they occurred, the reactions would be expected to be progressive and potentially severe.

HEPATOTOXIC POTENTIAL IN HUMANS

There is information that suggests that HCHO is associated with hepatotoxicity in humans. The data are limited, as well-controlled prospective epidemiological studies of the hepatotoxicity of HCHO in humans have not been done. The information is included in this article to give a perspective to the studies that were reviewed in the preceding sections and to illuminate possible areas of research.

Hayes et al. (1982) reviewed the hepatotoxic effects of 38 chemicals in animals and in humans. They found that for most of the cases in which histological or clinical chemistry changes occurred in humans and in animals, the changes were qualitatively similar. The most predictable hepatotoxic reactions were degenerative changes associated with the interaction of electrophilic intermediates with cellular macromolecules (Hayes et al., 1982). These findings would seem to apply to the data about HCHO, a highly reactive chemical which can combine with many body chemicals. The preceding sections reveal that exposure to HCHO is associated with effects on the liver of animals in various experimental situations. Consumer complaints and medical and legal records reveal several examples where the development of liver changes in humans is associated with exposure to HCHO. The following cases provide examples.

Mr. A. was a 55-yr-old male with a history of high blood pressure, high blood glucose, gout, and renal stones (U.S. District Court, 1982). To treat these conditions he took Zyloprim (allopurinol; 300 mg tid), Diuril (Chlorothiazide; 500 mg tid), Indocin (indomethacin; 50 mg tid), thyroid (5 g/d), Organidin (iodinated glycerol; 1 tablespoon PRN) and Anturane (sulfinpyrazone; 100 mg tid). Mr. A. took these drugs for over 2 yr before exposure to HCHO and had no indication of liver toxicity.

In April 1978, Mr. A. and his wife moved into a new mobile home. Soon thereafter, they developed headaches, itchy skin, and other symptoms of acute irritation/hypersensitivity that may follow exposure to HCHO (U.S. District Court, 1982). On June 15, 1978, Mr. A's direct bilirubin level was 0.6 units (the normal range for the laboratory was 0.2–0.4 units) and his lactic dehydrogenase (LDH) value was "high normal." Because the blood glucose concentration was also high, 250 mg tid of Diabenese (chlorproamide) was prescribed to Mr. A.

Between July 6 and July 12, the daily temperature outdoors exceeded 100°F. Four months later the U.S. Department of Labor, Office of Occupational Safety, used the National Institute of Occupational Safety and Health (NIOSH) chromatropic acid method to measure concentrations of 0.97 ppm HCHO in the mobile home. On July 12, Mr. A. became jaundiced and had clay-colored stools and orange-colored urine. Analyses of serum chemistry revealed abnormally high total bilirubin, alkaline phosphatase, glutamic oxaloacetic transaminase, and LDH concentrations. The concentration of cholesterol in serum remained unchanged from previous readings. A complete gall bladder and upper gastrointestinal X-ray series revealed the absence of gall stones or other blockages of the bile duct. Mr. A. was diagnosed by three physicians as having toxic hepatitis caused either by the drugs and/or by HCHO. Between July 25 and August 1, Mr. A moved out of the mobile home and recovered in 2 wk from the hepatitis. He later returned to the home for a few days, but moved out when he began to feel ill again (U.S. District Court, 1982).

Chlorpromamide causes choleostatic hepatitis in about 0.4% of people who take it (Larner and Haynes, 1975). Indomethacin and thyroid are also hepatotoxic (Zakin and Boyer, 1982; Zimmerman, 1978). The clinical signs and the chemistry data indicated that Mr. A. had a partial choleostatic response (perhaps from chlorpropamide) and a partial hepatotoxic response. The chronology of events indicates that exposure to HCHO was associated with the toxic hepatitis.

Another case illustrates the development of hepatitis in association with higher concentrations of HCHO, without exposure to drugs (U.S. District Court, 1983). J. B. was a healthy, 10-yr-old female in April 1980, when she and her mother and sister moved into a mobile home. Within 2 d, all family members experienced acute irritation due to HCHO in the home. Between June and July 1980, the family purchased a total of 4 pet birds, all of which died within 24 h after putting them in the mobile home. Over a period of 7 to 10 d in late August 1980, J. B. developed jaundice, fever, nausea, a slight pain in the upper right quandrant of the abdomen. She was hospitalized.

Clinical chemistry tests showed elevated SGOT and total and direct bilirubin concentrations in the serum and bilirubin in the urine. Because there was no history of exposure to viruses or other drugs or chemicals, she was diagnosed as having toxic hepatitis. She recovered quickly in the hospital and was sent home in 4 d. Within 1 wk she became ill again, but without hepatitis, and the family permanently moved out of the mobile home. In November 1980, the Department of Health, State of Texas measured, using Draeger tube analyses, 7 ppm HCHO in a storage area under the mobile home and 10 ppm in the living room. The air in the house was 87°F and the windows were closed. Subsequent analyses of serum for hepatitis B surface antigens and antibodies, hepatitis B core antigens and antibodies, and hepatitis A antigens and antibodies were conducted on two separate occasions. All values were negative; there was no evidence of infection of J. B. by A or B virus. Serum analyses done at the same times revealed no evidence of continuing liver disease (Central Medical Laboratory, Inc., 1982, 1983).

A limited number of occupational studies have also been performed. After one man died of HCHO poisoning following chronic exposure by inhalation, Spassowski investigated its toxicity in 113 of the deceased man's co-workers, who manufacture bakelite and adhesives from carbamide HCHO (Spassowski, 1965). The urine of 30 of these workers contained 2 to 4 times "a normal concentration of HCHO" (0.005 mg/l). In 16 of 31 other workers who showed skin hypersensitivity to HCHO, the urine contained an average of 40 mg/l. Twelve of the 16 workers showed delayed blood coagulation, which, according to Spassowski, suggested involvement of liver function.

Matanoski (1981) analyzed, by a log-linear regression model, the incidence of certain diseases in groups of radiologists and pathologists. Each group contained about 1500 people. Based on limited data, she found a significant excess of primary liver cancer in the pathologists compared to the radiologists. She also compared the disease incidences in a second group of experimental pathologists to the standard values for the U.S. white male population and again found a significant increase in primary liver cancer in the pathologists. Pathologists are commonly exposed to the tissue fixative formalin. However, its role in these cases of liver cancer is not known.

Repeated hepatic reactions to chemicals may, under some circumstances, lead to cirrhosis of the liver (Zakin and Boyer, 1982; Zimmerman, 1978). In rare cases, this may happen following exposure to HCHO over extended periods of time. In a recent epidemiological study, Levine (1982a, 1982b) examined the death certificates of 337 male undertakers in Ontario for several causes of death that might be associated with chronic exposure to HCHO. The incidences for various causes of death in the 309 undertakers were compared with those for a "control, normal" population. There was a significant increase in deaths related to nonmalignant diseases of the digestive tract ($p < 0.001$). Cirrhosis of the liver accounted for 18 of these deaths;

its incidence was significantly greater in the undertakers than it was in the control population (Ontario, SMR-172) (Levine, 1982a, 1982b). Levine (1982b) postulated that ethanol consumption is greater in Canadian undertakers than it is in "a normal population" and that ethanol caused the cirrhosis of the liver in the undertakers. We searched for, but did not find, data that show that the incidence of alcoholism in Canadian undertakers is greater than that in a normal population. There is, however, a medical case in which repeated exposure to HCHO was associated with chronic hepatitis, followed by cirrhosis of the liver and death (Palmero, 1982).

On December 14, 1976, Mrs. C. P., her husband, and their two children had urea-formaldehyde foam insulation (UFFI) installed in their home of 14 years. The next day all members of the family had symptoms of HCHO toxicity. None of the family members smoked. However, Mrs. C. P. had had a history of allergies. It included a reaction to penicillin in 1974 that required hospitalization. Within 3 d after the installation of UFFI, Mrs. C. P. had flu-like symptoms that required medical attention (Palmero, 1982).

In March 1977, Mrs. C. P. had multiple complaints that included jaundice and pain near the right costal margin. The family was advised by the poison center at the University of Connecticut that their illnesses were caused by HCHO and to move out of the house (Palmero, 1983, personal communication). In April 1977, the atmospheric concentration of HCHO in the home was between 10.0 and 15.0 ppm (Fleming, 1977; Palmero, 1982).

In May 1977, a medical evaluation revealed no blood or pulmonary abnormalities, but showed demographism and a swollen throat (Lanzi, 1980). Nevertheless, Mrs. C. P. continued to have "episodes" of respiratory difficulty and/or signs of systemic allergic reactions whenever she was exposed to situations associated with environmental chemical agents and odors (Mandell, 1977). For example, new clothes, household cleaners, cigarette smoke, and auto exhaust caused her breathing difficulties (Palmero, 1983, personal communication).

In the summer of 1977, she developed extreme breathing difficulties which threatened her survival and in 1979 her reactions included severe hepatitis (Palmero, 1982). There had been no history of prior liver disease, viral hepatitis, or alcoholism (Hom, 1982a). After 1979, her liver disease worsened and on April 29, 1982, Mrs. C. P. died from hepatic cirrhosis (Hom, 1982b; Chambers and Galvin, 1982).

SUMMARY AND CONCLUSIONS

The data in this review indicate that exposure to HCHO by inhalation, injection, or other avenues of contact is associated with liver changes in mice, rats, hamsters, guinea pigs, rabbits, dogs, and humans. Qualitative changes in the liver range from alterations in size and color to microscopic and biochemical manifestations. These qualitative changes do not seem to be species-, age-, or sex-specific. The lack of more pronounced changes following exposure to obviously toxic concentrations (about 38 ppm) in two studies underscores a need for additional research.

For several reasons, quantification of dose-response relationships between these hepatic changes and exposure requires additional information. For example, the purity of the test substance was not always reported and probably varied among the studies. Also exposure concentrations, or the methods used to measure them, were not always reported. Some of the hepatic changes were probably caused by secondary mechanisms, including passive hepatic congestion, serum pH fluctuations, or tissue damage at other sites within the test animals. Also, some of the less extensive or more commonly occurring changes, such as centrilobular vacuolization or mild necrosis, may have been underreported in studies that were not specifically designed to examine the hepatotoxicity of HCHO.

Although quantification of dose-response is not practical with the data reviewed, a qualitative pattern is suggested as one moves from effects occurring after acute exposure to greater amounts or concentrations of HCHO to those occurring after protracted exposure to lesser amounts. Acute exposure by inhalation to high concentrations of HCHO causes an increase in the size or weight of the liver within a few hours. Although the increase in weight could be due partly to passive congestion, it also involves swelling of hepatocytes and perhaps hepatic inflammation, hyperemia, and edema. The increase in liver weight is either accompanied by, or soon followed by, biochemical alterations such as clumping of nucleic acids and an increased concentration of hepatic alkaline phosphatase. Associated with these early changes may be hepatic inflammation or hyperemia and, within a few days, fatty infiltration and scattered necrosis.

After 2 to 3 wk of exposure, the effects on liver function may include a decrease in the formation and excretion of hippuric acid. Longer exposure to lower concentrations may cause similar effects. More prolonged exposure can lead to the development of hepatic necrosis, which may persist or be followed by regeneration, seen as focal hepatic hyperplasia (Fel'dman and Bonashevskaya, 1971). Other subchronic changes include coarsened and less dense RNA granules, changes in DNA, focal hypertrophy, decreases in hepatic ascorbic acid, and a decrease in the formation and excretion of hippuric acid.

After 6 mo of exposure to HCHO, the microscopic changes in the liver include centrilobular vacuolar degeneration, formation of cytoplasmic vacuoles, and hepatocellular degeneration. Although the nature of cytoplasmic vacuoles has not been defined, they may be due to fatty degeneration or to a depletion of liver glycogen, or both (Fischer, 1905; Gofmekler and Bonashevskaya, 1969; Swenberg, 1980b). Scattered areas of necrosis are also seen. These longer term changes are associated with a decrease in liver weight or a decrease in the ratio of liver weight to body weight, perhaps due to necrosis and loss of parenchyma, and in some instances macroscopic changes in the hepatic coloring and/or architecture. Limited evidence indicates that the hepatotoxic changes associated with HCHO in some individuals may develop into chronic disease, such as cirrhosis. This is of particular interest in light of the studies that demonstrate the development of anti-*N*-like antibodies in patients who are exposed directly to HCHO.

The hepatic effects associated with HCHO may result from some nonspecific mechanisms, such as changes in blood flow, pH, or the immune system. Formaldehyde may also induce hepatotoxicity through more direct metabolic mechanisms as well as through indirect means. Because HCHO may conjugate with various biological chemicals, it may reach the liver in an active form following inhalation. The need for GSH in the metabolism of HCHO and other chemicals raises the possibility of additive toxicity when medication is taken, or exposure to other chemicals occurs, in conjunction with exposure to HCHO. Clearly, more research is needed in these areas.

The data we reviewed indicate that exposure to 3.0 ppm or less for periods of up to 6 mo is not without effects and that higher exposures for shorter periods of time also have effects. Because humans may be exposed under similar conditions to formaldehyde, its role as a potential hepatotoxin in humans should be considered.

The data summarized in this article indicate that a relationship exists between exposure to formaldehyde and changes in the liver. However, additional research is needed to define this relationship and the human populations that may be affected by it.

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Item 4

Overview of Health Effects of Formaldehyde[1]

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[1] The opinions expressed in this article are those of the authors and do not necessarily reflect official positions or policies of the Consumer Product Safety Commission, Department of Energy, Veterans Administration, or the National Research Council.

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I. INTRODUCTION

Formaldehyde (H_2CO or HCHO),[2] first prepared by Butlerov in 1859, is today one of the most widely used chemicals in commercial production (*170*). In 1981, about 5.9 billion pounds of a 37% aqueous solution of formaldehyde (formalin) was produced in the United States. Approximately one-half of the annual production is used in the manufacture of urea–formaldehyde (UF) and phenol–formaldehyde (PF) resins for bonding of pressed wood products, especially plywood and particle board. Lesser amounts of UF resins are used in permanent press fabrics and, until recently, for UF foam insulation (UFFI). For a more detailed discussion of the chemistry, uses, and history of development of UF resins, see Meyer (*160*).

Formaldehyde is released by some wood and other products containing UF and related resins (*170*). Such formaldehyde initially may be present in small amounts in the manufactured product or may subsequently result from the hydrolysis of the UF resin bonding or coating the wood or other products. Wood

[2] Abbreviations: BCME, bis(chloromethyl) ether; CNS, central nervous system; $CV_{\%}$, closing volume expressed as percentage of the vital capacity; DEN, diethylnitrosamine; DNA, deoxyribonucleic acid; $FEF_{25-75\%}$, same as MMEF; $FEV_{1.0}$, forced expired volume in 1 sec; $FEV_{\%}$, $(FEV_{1.0} \div FVC) \times 100$; FH_4, tetrahydrofolic acid; FVC, forced vital capacity; GSH, glutathione; HCHO, formaldehyde; HMPA, hexamethyl phosphoramide; HMT, hexamethylenetetramine; HR, hexamethylenetetramine–resorcinol; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; $MEF_{50\%}$, maximum expiratory flow rate at 50% FVC; MMEF, maximum mid-expiratory flow calculated as the mean forced expiratory flow during the middle half of FVC; MMF, same as MMEF; NAD, nicotinamide adenine dinucleotide; PF, phenol–formaldehyde; PMR, proportionate mortality ratio; RE, reticuloendothelial; RNA, ribonucleic acid; SMR, standardized mortality ratio; TBA, tumor-bearing animals; TPA, tetradecanoylphorbol acetate; TLV, threshold limit value; TWA, time-weighted average; UF, urea–formaldehyde; UFFI, urea–formaldehyde foam insulation.

products containing UF resins emit more formaldehyde than wood products containing PF resins. Formaldehyde may be released also from UFFI, a product used for retrofitting insulation primarily in older structures (*45*). UFFI was made on site by mixing the liquid reactants and spraying them into small holes in the walls. Success with UFFI varied due to a number of factors that could not be predictably controlled. For example, mixing conditions of the liquid reactants and the temperature both were critical factors affecting the quality and at times resulted in poor formation of foam and release of unreacted formaldehyde. Even when the mixing conditions were ideal, some formaldehyde was released. The formaldehyde thus released permeated the walls into the living spaces wherein the occupants were exposed to concentrations that varied widely. Increasing numbers of consumers of formaldehyde-releasing products complained to both state and federal agencies about formaldehyde causing irritation of the eyes, nose, throat, and skin, and about persistent cough, dizziness, nausea, and headaches.

Many of the data on the noncarcinogenic effects of formaldehyde have been reviewed in the National Research Council's two reports (*169, 170*): one prepared by the Committee on Toxicology (1980) for the Consumer Product Safety Commission (CPSC) assessing the adverse health effects of formaldehyde (*169*), and the other by the Committee on Formaldehyde and Other Aldehydes in 1981 assessing the health and certain environmental effects for the Environmental Protection Agency (EPA) (*170*). Both these studies extensively reviewed the published literature on formaldehyde and discussed the irritation, the sensitization, and the other data on adverse health effects, but found a lack of adequate data to assess the risks of carcinogenicity. The reports pointed out that a substantial portion of the people exposed might react adversely even to low concentrations, and recommended that exposure be kept at the lowest practical concentration in indoor residential air.

In October 1979, concerns about the adverse health effects from exposure to formaldehyde grew considerably when the Formaldehyde Institute announced preliminary findings from the Chemical Industry Institute of Toxicology (CIIT) study of carcinogenicity in rats and mice experimentally exposed to formaldehyde gas. These findings, which are reviewed in more detail in Section X, showed that formaldehyde produced nasal squamous cell carcinomas in animals exposed to 14.3 ppm.[3]

Data on the mutagenicity, teratogenicity, carcinogenicity, and other chronic effects of formaldehyde were reviewed by the Federal Panel on Formaldehyde (a panel of 16 senior scientists established by CPSC and other agencies with the cooperation of the National Toxicology Program) (*70*). The panel concluded in its report that formaldehyde has been demonstrated to be mutagenic and carcinogenic under laboratory conditions and should be presumed to pose a cancer risk to humans, although data were not available for direct assessment in exposed humans. Similar conclusions were reached by the National Institute for Occupational Safety and Health (NIOSH) (*235*) and the International Agency for Research on Cancer (*117*).

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[3] Conversion factor: 1 ppm = 0.82 mg/m^3.

This article presents a review of the major findings of the available published research. The published literature on formaldehyde is too voluminous to be covered comprehensively in this overview. It is our intent therefore to characterize to the extent possible the adverse health effects of and the hazards posed by exposure to formaldehyde. To accomplish this objective, we shall discuss some of the relevant chemical reactions, sources of human exposure, its metabolism and metabolic fate, its irritation and sensitization properties, the carcinogenic, mutagenic, teratogenic, and reproductive effects, and what is presently known about epidemiologic studies, some of which are in progress.

II. REGULATORY ACTIVITIES

The state of California has banned the sale of urea–formaldehyde foam insulation (UFFI) unless the free formaldehyde content of the foam is less than 0.01% by weight. The city of Cincinnati, Ohio also has banned the installation of UFFI as have the states of Connecticut and Massachusetts. Installation of the product is banned for schools, nurseries, and certain other institutions in the state of Colorado. The states of New Hampshire and New York require that installers of UFFI warn potential buyers of the potential health effects of formaldehyde. The states of Minnesota and Wisconsin have established standards of 0.5 and 0.4 ppm, respectively, for formaldehyde levels in mobile homes. The state of Texas requires that retailers or manufacturers of mobile homes warn consumers of the potential health effects of formaldehyde. On the national level, installation of UFFI was banned in residences and schools by the CPSC on August 9, 1982. The ban was overturned by the Fifth Circuit Court of Appeals in April 1983, and the Commission's request for reconsideration was denied in June 1983. The Commission's request to the Justice Department to appeal the case to the Supreme Court was turned down in September 1983 despite numerous scientific errors contained in the Fifth Circuit decision.

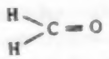
With regard to other residential standards and guidelines, the American Society of Heating, Refrigeration, and Air Conditioning Engineers (ASHRAE) has recommended that formaldehyde levels not exceed 0.1 ppm. Denmark, The Netherlands, and West Germany have residential standards for formaldehyde of 0.12, 0.10, and 0.10 ppm, respectively.

III. CHEMICAL PROPERTIES

A. Chemical Forms

1. Monomeric Formaldehyde

Formaldehyde is a colorless gas that is usually manufactured by reacting methanol vapor with air in the presence of a catalyst. It is designated by its molecular formula HCHO or the structural formula

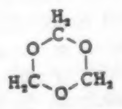


Commercially, it is not available in the monomeric form but is commonly sold as an aqueous solution of from 30 to 56% formaldehyde by weight with from 0.5 to 15% methanol added to prevent polymerization.

It has a characteristic pungent, suffocating odor, and it is highly irritating to exposed membranes of the eyes, nose, and respiratory tract. Some of its physical properties are density, 1.067 (air = 1.000); vapor pressure, 400 mm Hg at 33°C; flash point, 430°C; boiling point, −19°C; and melting point, −118°C. In addition, formaldehyde polymerizes slowly at temperatures below 80–100°C.

2. Trioxane

Formaldehyde is available commercially also as the cyclic trimer trioxane (trioxymethylene), designated by the molecular formula $C_3H_5O_3$ or the structural formula



In pure form, trioxane is a colorless crystalline solid that has a nonirritating chloroformlike odor. It boils at 115°C and melts at 61–62°C.

3. Paraformaldehyde

This commercial form of formaldehyde is a colorless solid prepared by condensation of methylene glycol (methanediol) and is designated by the formula $HO—(HCHO)_8—H$. It has the same characteristic odor as monomeric formaldehyde and melts over a wide temperature range (120–170°C). Thus, heating paraformaldehyde on a hot plate releases formaldehyde. This is a procedure commonly used for disinfecting large areas.

B. Chemical Reactivity

Polymerization of double-bonded methylene compounds and of simple methyl derivatives is the principle mechanism by which formaldehyde reacts with other chemicals to form some of the resinous products mentioned elsewhere in this article.

It is beyond the scope of this article to discuss in depth all of the chemical reactions involving formaldehyde. The reactions given below were selected to show some of the more important ways in which formaldehyde reacts with other chemicals.

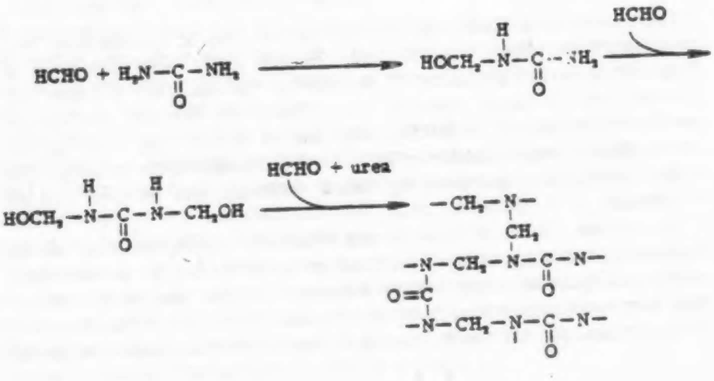
1. Industrial Preparation

Although cheaper reagents may be used by manufacturers, the general method for preparation of formaldehyde from alcohols (methanol) is oxidation with air or dehydrogenation over hot copper or silver catalyst. For example:

$$CH_3OH \xrightarrow[\Delta]{Cu} HCHO + H_2$$

2. Reaction with Urea

Formaldehyde's high degree of chemical reactivity has been attributed to the direct attachment of the carbonyl carbon to two hydrogen atoms. It is because of this strongly reducing reactivity that it has found widespread commercial use in reactions with urea and resinous substances to produce a wide variety of products. This abbreviated illustration shows the basic reaction used in forming the urea–formaldehyde polymer.



3. Reaction with Hydrochloric Acid

This reaction is important owing to the possible formation of the known carcinogen bis(chloromethyl) ether where human exposure to both chemicals may occur.

$$2HCHO + 2HCl \rightarrow ClH_2C{-}O{-}CH_2Cl + H_2O$$

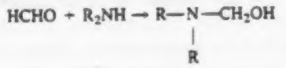
4. Reactions of Biological Interest

The following reactions of formaldehyde are important since they can involve nucleic acids, proteins, and other amine-containing molecules within the cell.

Hydration:

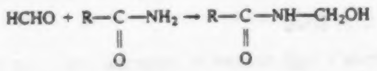
$$HCHO + H_2O \rightarrow CH_2(OH)_2$$

Amines:



$$HCHO + R_2NH \rightarrow R{-}\underset{R}{\underset{|}{N}}{-}CH_2OH$$

$$HCHO + RNH_2 \rightarrow R{-}NH{-}CH_2OH$$



$$HCHO + R{-}\underset{O}{\underset{\|}{C}}{-}NH_2 \rightarrow R{-}\underset{O}{\underset{\|}{C}}{-}NH{-}CH_2OH$$

$$R{-}NH{-}CH_2OH + RNH_2 \rightarrow R{-}NH{-}CH_2{-}NH{-}R + H_2O$$

Acetal:

$$HCHO + ROH \rightarrow R{-}O{-}CH_2OH$$

IV. SOURCES AND EXPOSURE

The sources of formaldehyde to which humans may be exposed have been reviewed extensively (*44, 45, 160, 169, 170, 229, 230*). These sources can be divided into two basic classes: (1) commercial manufacturing processes and products, and (2) natural processes. For 1978, it was estimated that approximately 68% of the total formaldehyde production of 1,580,000 × 10^3 kg was due to commercial processes; natural processes accounted for the remainder. All of the formaldehyde produced by natural processes was released into the atmosphere.

The primary sources of formaldehyde released by natural processes are the incomplete combustion of fossil fuels and refuse (65%) and the photochemical oxidation of hydrocarbons released by automotive exhaust. Sources of formaldehyde from combustion processes outdoors include incinerators, refineries, power plants, houses, and businesses, as well as automobile, bus, truck, and jet exhausts. The amount of formaldehyde released in automobile exhaust has been decreasing steadily with the increasing use of catalytic converters. Gas stoves, ovens, and unvented heaters are major indoor combustion processes that are sources of formaldehyde.

Almost all (94%) commercially produced formaldehyde goes into the manufacturing of various resins and plastics. The remaining 6% is used for embalming fluid and tissue fixation, and as a preservative in various products. Over half (55%) of all commercially produced formaldehyde is used to produce urea–formaldehyde and phenol–formaldehyde resins.

Most of the urea–formaldehyde (UF) resins produced (28% of commercial formaldehyde production) are used as bonding agents in the manufacture of products such as interior grades of plywood, particle board, and fiber board, and for paper and textile treating and coating resins, protective coatings, and laminates. Additionally, until banned by the CPSC in August 1982, a small amount of UF resin production was used to make urea–formaldehyde foam insulation for homes, schools, and commercial buildings (*70*). Press time, temperature, and moisture content influence the release of formaldehyde from wood products as do ambient humidity and temperature loading and background levels of formaldehyde. Release of formaldehyde from urea–formaldehyde foam insulation is affected by temperature and humidity, age of chemicals, mixing of components, and other factors.

Phenol–formaldehyde (PF) resins are produced in quantities approximately equal to urea–formaldehyde resins. They are used as adhesives for exterior grades of plywood and particle board, and as friction material, foundry and shell moldings insulation, molding compounds, protective coatings, and laminates. The release of formaldehyde from PF products using PF resins is much less than that from those containing UF resins. Meyer (*160*) has estimated that PF resins are 1000 times more stable than UF resins.

Formaldehyde is used also to produce melamine and acetal resins (11% of commercial formaldehyde production). These resins are used predominantly in plastics and molding compounds; release of formaldehyde from products using these resins is considered negligible.

Other uses of formaldehyde include production of the chemical intermediates pentaerythritol, 1,4-butanediol, trimethylpropane, and hexamethylenetetramine (HMT). Production of these chemicals consumes approximately 20% of commercial formaldehyde. It is uncertain how much formaldehyde is released by products synthesized from these chemicals.

Formaldehyde (or a derivative) is used at low concentration as a disinfectant and preservative in a variety of cosmetics, including shampoos, makeup, eyeshadow, and bubblebath. Formaldehyde is used also for the preservation and hardening of biological specimens and as a topical fungicide. A partial listing of products containing formaldehyde is shown in Table I.

TABLE I

Product Uses of Formaldehyde

- Adhesives
- Concrete
- Cosmetics
- Deodorants
- Detergents
- Dry cleaning solutions
- Dyes
- Embalming fluids
- Explosives
- Fertilizers
- Fiberboard
- Food
- Food packaging materials
- Friction materials
- Fuels
- Fungicides
- Furniture
- Insulation and fiberglass
- Intermediate chemicals
- Laminates
- Leathers
- Lubricants
- Mothballs
- Paints
- Paper
- Polishes
- Photographic developing solutions
- Particleboard
- Pharmaceuticals
- Plastics
- Plywood
- Rubber
- Textiles
- Water softening chemicals

Many formaldehyde-containing products have the ability to release formaldehyde during and after manufacture, thereby exposing workers and consumers to the chemical. These data, although not extensive for many exposure settings, indicate that exposure is widespread and can be significant for certain populations. Table II identifies the sources of human exposure to formaldehyde and provides an estimation of the size of each subpopulation, the mean exposure level and standard deviation to which each is exposed, and the duration of exposure in hours per week.

Although data are limited, workers in many different occupations can be exposed to formaldehyde. Formaldehyde production workers, resin production workers, veneer panel production workers, textile workers, embalmers, and pathologists appear to be exposed to higher concentrations of formaldehyde than other types of workers.

The most extensive data bases exist for two types of consumer exposures. These are houses that have been insulated with UFFI and mobile homes.

Houses with UFFI have been found to have significantly higher formaldehyde concentrations than non-UFFI homes (*70*). On the basis of data collected on UFFI installed in panels under near ideal conditions, it has been estimated that UFFI at 25°C can contribute 0.05–0.4 ppm to the formaldehyde burden of the home. When similar panels were tested at 23, 33, and 40°C (temperatures that may be encountered in wall cavities), the average concentration of formaldehyde emitted from the panels increased 6-fold at 33°C and 13-fold at 40°C, compared to that emitted at 23°C. Emission may continue over a period of several years.

TABLE II

Human Exposure to Formaldehyde[a]

Exposure source	Estimated number exposed	Number of observations	Mean exposure level (ppm) ± standard deviation	Estimated duration (h/week)
I. Occupational				
A. Direct production of formaldehyde	420	3	1.34 ± 0.27	40
B. Commercial use of formaldehyde and formaldehyde products				
1. Urea–formaldehyde foam installers	2,000–15,000	42	0.25 ± 0.09	40
2. Manufacturers				
a. Resin producers	2,000–45,000	165	0.31 ± 0.04	40
Urea–formaldehyde foam producers	30–80	28	0.68 ± 0.41	40
b. Molded products producers	Unknown	88	0.23 ± 0.04	40
c. Furniture, production of veneered panels	Unknown	41	0.92 ± 0.36	40
d. Textile producers	360–6,000	84	0.54 ± 0.09	40
e. Textile storage	Unknown	22	0.28 ± 0.08	40
f. Fertilizer producers	500–900	11	0.82 ± 0.35	30
3. Others				
a. Embalmers	70,000	12	1.04 ± 0.36	20
b. Pathologists	12,000	11	2.79 ± 1.45	30

c. Biology instructors	35,000	21	0.32 ± 0.17	20
d. Students				
College/university	1,200,000	21	0.32 ± 0.17	1
Medical school	60,000	7	1.56 ± 0.74	15
High school	Unknown	21	0.32 ± 0.17	1
II. Residential and commercial building levels, use of				
A. Plywood/particle board				
1. Conventional homes				
a. Denmark	Unknown	25	0.53 ± 0.15	100–150
b. United States	Unknown	12	0.28 ± 0.16	100–150
2. Mobile homes	2,200,000	836	0.37 ± 0.02	100–150
B. Urea-formaldehyde foam insulation				
1. Homes	1,750,000	751	0.12 ± 0.02	100–150
2. Shopping center, offices, and stores	Unknown	66	1.17 ± 0.41	40
III. Ambient levels				
A. Air	220,000,000	41	0.02 ± 0.018	168
B. Non-UFFI homes	Unknown	51	0.03 ± 0.004	100–150

[a] From Ulsamer *et al.* (230).

Mobile homes, which use particle board and plywood extensively in their construction, are well insulated (but not with UF foam insulation) and are relatively air tight. Mobile homes were found to contain an average of 0.37 ppm of formaldehyde (*230*). Levels in new homes were higher than those in older homes. Emission may continue for a period of years.

V. METABOLISM

Formaldehyde is an important intermediate in the biosynthesis of amino acids, lipids, and nucleotides. It also alkylates nucleic acids and proteins and is converted to formate and CO_2 (Fig. 1). Following acute inhalation exposure, formaldehyde gas is absorbed primarily via the upper respiratory tract in dogs (*63*) and in rats (*223*). Formaldehyde can penetrate into the lower respiratory tract when adsorbed to particulates (*5*, *6*).

When rats inhaled [^{14}C]formaldehyde, nasal tissues were found to contain the highest concentration (10- to 100-fold greater than other tissues) of radiolabel; most of the isotope remaining in the body was distributed throughout body tissues (*102*, *103*). The chemical form of the radiolabel was not defined but, based on what is known about formaldehyde's chemical reactivity and metabolism, it is unlikely that any of the radiolabel remained as formaldehyde.

Dermal absorption of [^{14}C]formaldehyde has been demonstrated in several species of laboratory animals, including rats and monkeys (*118*), guinea pigs (*236*), and rabbits (*195*). The chemical form of the radiolabel has yet to be determined but preliminary data from *in vitro* diffusion studies using rabbit skin (*100*) indicate that formaldehyde per se cannot be detected enzymatically.

Formaldehyde that enters the body is rapidly metabolized to formate. Intravenous (iv) infusion of formaldehyde into dogs demonstrated that formate levels in blood rapidly increased whereas formaldehyde could be detected only during infusion (*148*). The rapidity of this conversion was demonstrated by the finding that the peak in blood formate concentration occurred within the same time frame, and was of the same magnitude, regardless of whether formaldehyde or sodium formate was infused into dogs. The plasma half-life of formate was also the same following injection of either chemical (between 80 and 90 min). Following infusion of formaldehyde into cynomolgus monkeys, the half-life of the formaldehyde in the blood was estimated to be 1.5 min (*157*). Similar estimates of half-life have been made for cats, guinea pigs, rabbits, and rats (*194*). More recently, Heck (*102*) has shown that [^{14}C]formate distributes similarly to [^{14}C]formaldehyde in rat blood cells and plasma following iv injection, and follows the same decay curve.

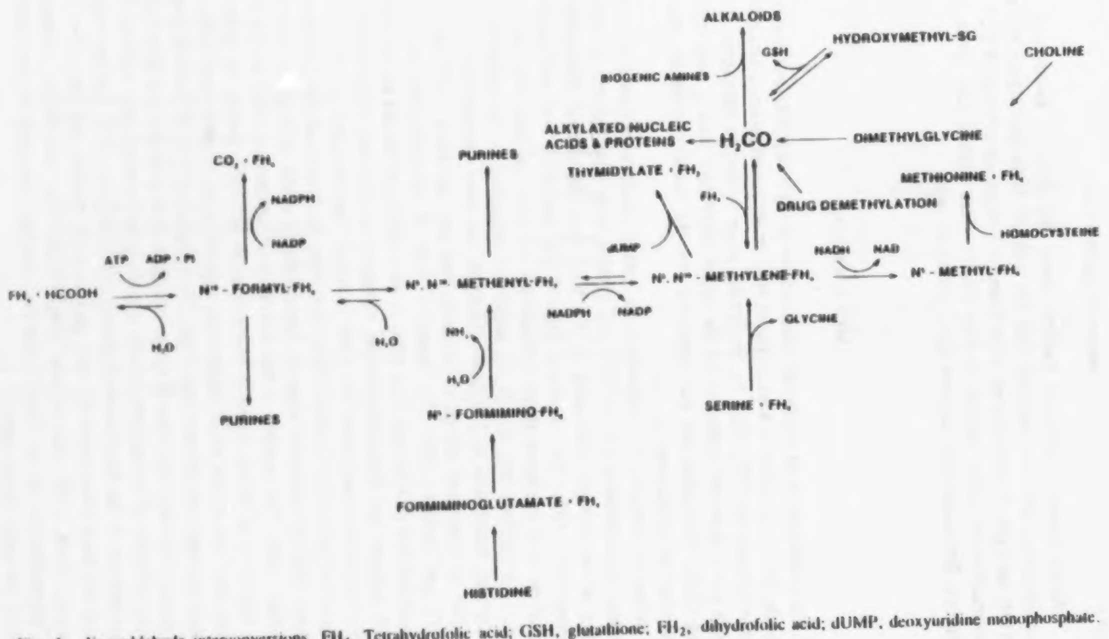

ALKALOIDS
GSH
HYDROXYMETHYL-SG
CHOLINE
BIOGENIC AMINES
ALKYLATED NUCLEIC ACIDS & PROTEINS
H_2CO
DIMETHYLGLYCINE
PURINES
$CO_2 \cdot FH_4$
THYMIDYLATE · FH_2
METHIONINE · FH_4
NADPH
FH_4
DRUG DEMETHYLATION
NADP
dUMP
HOMOCYSTEINE
ATP
ADP · Pi
NADH
NAD
$FH_4 \cdot HCOOH$
N^{10} - FORMYL-FH_4
N^5, N^{10}- METHENYL-FH_4
N^5, N^{10} - METHYLENE-FH_4
N^5 - METHYL-FH_4
NADPH
NADP
GLYCINE
H_2O
H_2O
NH_3
H_2O
PURINES
N^5 - FORMIMINO-FH_4
SERINE · FH_4
FORMIMINOGLUTAMATE · FH_4
HISTIDINE

Fig. 1. Formaldehyde interconversions. FH_4, Tetrahydrofolic acid; GSH, glutathione; FH_2, dihydrofolic acid; dUMP, deoxyuridine monophosphate.

Several studies have described the metabolic fate of formaldehyde once it enters the body. DuVigneaud *et al.* (*60*) found that approximately 80% of subcutaneously (sc) administered formaldehyde is converted to CO_2, while a small amount remained in body tissues incorporated into choline. Neely (*172*) administered [^{14}C]formaldehyde intraperitoneally (ip) to rats at doses of 7 and approximately 70 mg/kg. At the higher dose, 82% of the radiolabel was expired as CO_2 after 24–48 h and 14% was recovered in the urine. Most of the radiolabel in the urine was found to be incorporated into methionine and a cysteine adduct with lesser amounts as serine and "formaldehyde." "Formaldehyde" was determined by a chemical method of analysis. Since no radiolabeled peak corresponding to formaldehyde could be detected when a sample of urine was chromatographed, "formaldehyde" may be an artifact resulting from cleavage of a conjugate during chemical analysis. Neither the cysteine adduct nor serine could be detected following administration of the 7 mg/kg dose. The nature of the cysteine adduct was not defined, but Neely found that a chromatographically identical product could be formed by adding formaldehyde to cysteine or to urine. Edwards *et al.* (*61*) identified the cysteine adduct as *N*-formylcysteine in rats and mice following ip administration of [^{14}C]formaldehyde. Methionine and serine were also found in the urine of both species. The reaction of formaldehyde with cysteine occurs nonenzymatically and in preference to that with glutathione (GSH) (*97*). More recently, Mashford and Jones (*155*) demonstrated that in rats administered 4 mg/kg of formaldehyde ip, 82% of the dose was exhaled within 48 h as CO_2, while 5.5% was excreted in the urine. At 40 mg/kg, 78% of the dose was exhaled as CO_2 after 48 h and 11% was excreted in urine. The metabolites in urine were the same at either dose: *N*-(hydroxymethyl)urea, *N,N'*-bis(hydroxymethyl)urea, and formate. The authors postulated that the urea conjugates are formed in the urine by chemical reaction with free formaldehyde, and that 3–5% of the higher dose may therefore have been excreted in the urine as free formaldehyde; no formaldehyde was found in expired air. It is uncertain whether the formaldehyde in the urine is free or exists in the form of a labile conjugate. The excretion of formate contrasts with results obtained by other investigators and may be related to the strain of rat used. When formaldehyde is inhaled by F344 rats (*102*), rather than injected, 40% of the radiolabel is retained in the animal, while 40% is exhaled and 20% appears in the urine. In the nasal mucosa of these rats, RNA contained the greatest amount of radiolabel with a lesser amount in protein and a small amount in DNA (*103*). In WI-38 human fibroblasts exposed to [^{14}C]formaldehyde, most of the radiolabel is incorporated into RNA with lesser amounts in DNA and protein (*190*). The purine bases of the nucleic acids were labeled most heavily. Formate appeared rapidly in the blood and urine of humans exposed to formaldehyde gas (*64*). Einbrodt also found a small amount of formaldehyde in the urine by chemical analysis but this may have resulted from the breakdown of a labile conjugate. Eels *et al.* (*62*) noted a rise in formate in the blood following ingestion of formalin by a 41-year-old woman. In addition to being converted rapidly to formate and CO_2 as well as being incorporated into various body chemicals formaldehyde also can alkylate amino acids, such as cysteine (*107*) and lysine (*228*), proteins (*72, 215*), nucleotides (*107*), and DNA (*36, 72*). The reaction of formaldehyde with DNA to form stable linkages is enhanced by the presence of amino acids (especially lysine) and histones (*215*). Linkages between protein and DNA have been reported in formaldehyde-exposed rats (*101*) and in mouse leukemia L1210 cells (*196*).

The conversion of formaldehyde to formate is catalyzed by formaldehyde dehydrogenase (*231*). This enzyme catalyzes an easily reversible reaction between GSH, formaldehyde, and NAD to yield *S*-formylglutathione. The actual substrate for formaldehyde dehydrogenase is probably the hemimercaptal of formaldehyde and GSH which forms nonenzymatically (*238*). Hydrolysis of *S*-formylglutathione to formic acid and GSH is catalyzed by *S*-formylglutathione hydrolase (*232*). This reaction is described as being very fast, highly specific, and apparently irreversible; it is not inhibited by formate. In human liver, hydrolase activity is present in great excess over formaldehyde dehydrogenase activity. Both enzymes are of cytoplasmic origin in liver (*204, 231, 232*). Human erythrocytes (*148*) and brain, sheep liver, rat brain, kidney, and muscle, rabbit brain, and bovine brain and adrenal (*232*) also can rapidly convert formaldehyde to formate. In human liver, *S*-formylglutathione can be hydrolyzed also by glyoxalase II to formic acid and GSH (*232*). The authors noted that the activity of this enzyme is equivalent to that of formaldehyde dehydrogenase in liver. Formaldehyde is also oxidized to formic acid by a nonspecific aldehyde dehydrogenase and by the tetrahydrofolic acid (FH_4) pathway (*115*). The aldehyde dehydrogenase that oxidizes formaldehyde to formate is found primarily in mitochondria of liver cells; the microsomal aldehyde dehydrogenase has not been found to be reactive with formaldehyde (*133*).

Formaldehyde, as well as formate, is converted to CO_2. This can occur via the FH_4 pathway (Fig. 1) or via deamination of serine (formed from formaldehyde) to form pyruvate, which is then oxidized to CO_2 by the mitochondria. Finally, formate can be converted to CO_2 via catalase, but this pathway is apparently of much less importance than the FH_4 pathway (*157, 181, 244*). Den Engelse *et al.* (*57*) have shown that lung is less efficient than liver in converting formate to CO_2.

Formaldehyde that enters the FH_4 pathway does so by nonenzymatic reaction with FH_4 to form an N^5-carbinolamine (*126*). The carbinolamine proceeds rapidly through an imine to N^5,N^{10}-methylene-FH_4 in a reaction with an equilibrium constant of approximately 10^4 in favor of the formation of the end product (*126, 177*). The equilibrium constant for the dissociation of N^5,N^{10}-methylene-FH_4 has been reported to be 3×10^{-5} (*21*). The reaction is inhibited by thiols, such as 2-mercaptoethanol, which react preferentially with formaldehyde (*126*).

The efficiency of these processes in metabolizing formaldehyde was demonstrated by the infusion studies discussed above (*148*, *157*, *194*). A more recent study by Heck *et al.* (*104*) has actually quantitated labile formaldehyde in various tissues of F344 rats before and after inhalation of either formaldehyde or chloromethane. The method used by Heck measures both free and bound formaldehyde (the formaldehyde derivatives of both glutathione and FH_4 react) without distinguishing between the two forms. "Labile formaldehyde" levels range from 0.42 μmol/g for nasal mucosa to 0.097 μmol/g for brain; liver contains 0.20 μmol/g. Inhalation of 6 ppm of formaldehyde for 6 h/day for 10 days did not significantly alter the concentration of labile formaldehyde in the nose (the only tissue measured postexposure). A similar finding was made following inhalation of 15 ppm of formaldehyde (*103*). Glutathione levels were likewise unchanged following inhalation of 15 ppm of formaldehyde in this study. Previous work from the same laboratory demonstrated that CO_2 production from inhaled formaldehyde is directly proportional to dose at 0.5 and 13.1 ppm in rats (*86*). When chloromethane was inhaled by rats, the formaldehyde concentrations in liver and testes approximately doubled while increasing sevenfold in brain; no data were given for the nose (*194*). Whether this increase represents formation of a conjugate not seen when formaldehyde itself is inhaled or whether it is related to depletion of GSH as postulated by the author is unclear.

Formaldehyde in tissue can result from a number of sources. The primary source of endogenous formaldehyde is the degradation of serine (*15*) with some contribution from the degradation of other amino acids (see Fig. 1). Oxidative demethylation of *N*,*N*-dimethylglycine (from choline degradation) also contributes significantly to endogenous formaldehyde. Cytochrome *P*-450-dependent N-demethylation of drugs can contribute additional formaldehyde (*1*, *244*). Using aminopyrine as the substrate for the demethylation reaction, Waydhas *et al.* (*244*) found that the rate of formaldehyde oxidation to formate exceeded the rate of formaldehyde production in perfused rat liver by a factor of 12. Other xenobiotics including dihalomethanes (2), methanol (*157*), dimethylnitrosamine (*119*), hexamethylphosphoramide (HMPA) (*50*), bis(chloromethyl) ether (BCME) (*213*), dibromoethane (*130*), and dimethylsulfoxide (*131*) lead to the production of formaldehyde. Formaldehyde is also formed *in vitro* in the presence of an amine acceptor, apparently by nonenzymatic breakdown of N^5,N^{10}-methylene-FH_4 (*137*, *140*, *226*). This reaction produces alkaloids from biogenic amines or drugs *in vitro* and probably *in vivo* (*145*). Formaldehyde resulting from the metabolism of HMPA, and dibromoethane (*50*), dimethylnitrosamine (*119*), and bis(chloromethyl) ether (*213*) may be the active species for these carcinogens. Using rat liver microsomes, formaldehyde production and accumulation could be demonstrated from HMPA (*50*) and dimethylnitrosamine (*119*). The accumulation of formaldehyde in microsomal preparations is not unexpected since microsomes have no detectable aldehyde dehydrogenase of the type capable of oxidizing formaldehyde (*133*), whereas formaldehyde dehydrogenase is primarily cytoplasmic in origin (*231*). Dodd *et al.* (*58*) have shown that labile formaldehyde also accumulated *in vivo* in tissues following inhalation of chloromethane. In contrast, when monkeys were administered methanol (which also metabolized to formaldehyde) by a nasogastric tube, no increase in formaldehyde concentrations could be detected in body tissues (*157*). Alcohol dehydrogenase, which converts methanol to formaldehyde, is cytoplasmic in origin (*185*) as is formaldehyde dehydrogenase. These findings raise the possibility that formaldehyde derived from xenobiotics metabolized by the microsomes may lead to accumulation of formaldehyde conjugates in tissue and pose a greater risk of carcinogenicity than formaldehyde derived from xenobiotics metabolized in the cytoplasm.

Exposure to formaldehyde may also cause additive toxicity to that caused by chemicals that require glutathione for detoxification (*136*). Chemicals with the potential for additive toxicity by this mechanism are numerous and include acetaminophen and corticosteroids (*52, 53, 128, 147*). Exposure to these chemicals may increase during periods when toxic exposure to formaldehyde occurs since they could be used to treat acute symptoms, such as headaches and skin rashes.

VI. GENERAL TOXICOLOGY

The acute toxicity of formaldehyde has been studied in several animal species by different routes of administration. The reported LD_{50} and LC_{50} values are summarized in Table III. These studies indicate that when formaldehyde is

TABLE III

Acute Toxicity

Species/ strains	Medium tested	Route	Observation period	Measure	Reference
Rats	2% solution	po	14 days	LD_{50}, 800 mg/kg	*217*
Guinea pigs	2% solution	po	14 days	LD_{50}, 260 mg/kg	*217*
Albino mice	Vaporized aqueous solution	Respiratory	45 days	LT_{50}, 100 min. (320 ppm)	*19*
Rabbit	Solution	Dermal	—	LD_{50}, 270 mg/kg	*144*
Rat	Solution	iv	—	LD_{50}, 87 mg/kg	*141*
Rat	35.5% solution	sc	—	LD_{50}, 420 mg/kg	*216*
Mice	35.5% solution	sc	—	LD_{50}, 300 mg/kg	*216*
Rat	35.5% solution	Respiratory	—	LC_{50}, 1.0 mg/liter (830 ppm), 30 min	*216*

TABLE IV

Lowest Effective Concentration of Formaldehyde: Human and Animal Controlled Studies[a]

Concentration (ppm)	Length of exposure	Species	Effect	Reference
0.01	5 min	Human	Eye irritation	*206*
0.05–0.06	Minutes	Human	Odor threshold	*71, 159, 237*
0.07	Minutes	Human	Optical chronaxy threshold	*159*
0.08	1.5 months	Rabbit	Changes in evoked potential of optic nerve	*23*
0.08	Minutes	Human	Threshold to affect the functional state of cerebral cortex	*159*
0.2	1 h	Human	Eye, nose, and throat irritation	*192*
0.25	5 h	Human	Dryness of nose and throat, decrease in mucous flow rate	*9*
0.31	1 h	Guinea pig	Increased airway flow resistance, decreased compliance	*5*
0.55	10 min	Rat	Reduction in respiratory rate	*127*
0.83	3 months	Rat	Histologic and histochemical changes in cerebral amygdaloid complex	*24*
0.83	1 min	Human	Altered functional state of cerebral cortex	*71*
0.83	90 days	Rat	Peribronchial and perivascular hyperemia, lymphohistiocytic proliferation in lung, focal hyperplasia and RE system activation in liver and changes in cerebral cortex	*71*
0.83	10 min	Human	Irritation of upper tract and eyes, accelerated breathing, EEG changes such as alpha rhythm enhancement, changes in automatic nervous system	*209*

0.83	10 months over two generations	Rat	Morphological changes in upper respiratory tract, decreased liver weight	*161*
0.83	Continuous, beginning 10–15 days before mating	Rat	Increase in size and number of extramedulary hematopoietic centers, increased epithelial proliferation of common bile duct, increased abnormalities of renal epithelium	*88*
1.4	1 min	Human	Eye sensitivity to light lowered in unacclimated group	*159*
1.67	Continuous or intermittent	Guinea pig, rat	Sensitization (inhalation), leukocytosis, and change in blood cholinesterase	*178*
2	6 h/day, 5 day/week for 18 months	Rat	Epithelial hyperplasia, squamous cell metaplasia of nasal turbinates, rhinitis	*223*
3.8	90 days continuous	Rat, dog, rabbit, monkey, guinea pig	Death in 1/15 rats, some inflammation of lungs in all species	*45a*
4.1	1 h on days 1–19 of gestation	Rat	Increase in threshold of neuromuscular excitability, peripheral white blood cells, decreased hemoglobin and rectal temperature in pregnant animals	*211*
4.2	1 min	Human	Unbearable without respiratory protection	*246*
15.5	10 h	Mouse, rabbit, guinea pig	5/7 mice, 3/5 rabbits, 8/20 guinea pigs dead; closed eyes, slow deep respiration, convulsions	*201*
41.5	1 h/day, 3 day/week for 35 weeks	Mouse	Upper respiratory tract inflammation, basal cell hyperplasia, epithelial stratification, bronchopneumonia	*113*
482	4 h	Rat	LC_{50} (approximate)	*168*

[a] From Gupta *et al.* (*94a*), with permission.

administered by subcutaneous or intravenous injection to rats it is more lethal than when administered orally. This may be because formaldehyde reacts with chyme, thus decreasing the amount available for absorption. The effects observed following exposure of experimental animals and humans to formaldehyde by inhalation include tissue irritation, sensitization, and CNS effects (*169, 170, 233, 234*). These effects, summarized in Tables IV and V [from Gupta *et al.* (*94a*)], include eye, nose, throat, and pulmonary irritation and hyperemia, skin

TABLE V

Human Occupational and Residential Studies: Ranges of Formaldehyde Concentrations Giving Adverse Effects[a]

Concentration (ppm)	Effect	Type of exposure	Reference
0.01–10	Nausea; eye, nose, and throat irritation; headache; vomiting; stomach cramps	Residential	*44*
0.02–4.15	Diarrhea, eye and upper respiratory tract irritation, headache, nausea, vomiting	Residential	*29, 85, 203, 249*
0.09–5.6	Burning of eye and nose; sneezing, coughing, and headaches; 3 out of 7 suffered from asthma or sinus problems	Occupational	*129*
0.3–2.7; mean, 0.68; median, 0.4	Annoying odor, constant prickling of mucous membranes, disturbed sleep, thirst, heavy tearing	Occupational	*212*
0.13–0.45	Burning and stinging of eyes, nose, and throat; headaches	Occupational	*27*
0.83	Loss of olfactory sense, increased upper respiratory disease, subatrophic and hypertrophic alterations in nose and throat, ciliostasis of nasal mucosa, increased absorptive function of nasal mucosa	Occupational (greater than 5 years to less than 10 years)	*250*
0.9–1.6	Itching eyes, dry and sore throats, disturbed sleep, unusual thirst upon awakening in morning	Occupational	*164*
0.9–2.7	Tearing of eyes, irritation of nose and throat	Occupational, 1966	*22*
Unknown	Chronic airway obstruction, respiratory tract and eye irritation, small decrease in pulmonary function during workday and workweek	Occupational	*205*
1.3–3.8	Menstrual disorders, pregnancy complications, low birth weight of offspring	Occupational	*214*
4 or less	Inflammation, reactions of upper respiratory tract, chronic bronchitis, conjunctivitis, and skin changes	Occupational (7-year mean exposure)	*134*

[a] From Gupta *et al.* (*94a*), with permission.

rashes, changes in cerebral cortex, development of headaches, and many other effects.

In many instances, the changes that occur in animals that are exposed to formaldehyde are similar to those that occur in humans who are likewise exposed. This may be illustrated by the effects on the airways. Amdur (*5, 6*) exposed guinea pigs to formaldehyde and found, even at 0.07 ppm in the presence of NaCl particles, significantly increased airway resistance and decreased lung compliance. Murphy *et al.* (*167*) noted similar changes after exposure to higher concentrations of formaldehyde in rats; they also found signs of eye and nasal irritation, dyspnea, and an increase in liver alkaline phosphatase. When exposed to low concentrations of formaldehyde, humans often experience nose and throat irritation (*8, 169, 170*). In humans, pulmonary irritation may be characterized by cough, a feeling of tightness in the chest, and wheezing (signs of bronchial constriction) (*84, 169, 170, 189*). A protective mechanism against the respiratory effects of inhaled formaldehyde appears to exist in mice, which are able to decrease their respiration rate by up to 50% when exposed to formaldehyde (*127*). Barrow (*12*) also reported similar results in mice and to a lesser extent in rats. Formaldehyde is also a severe eye irritant in rabbits (*35*) and in humans (*8, 192*). Significantly, humans experience conjunctival irritation when exposed to as little as 0.20 ppm of formaldehyde alone (*192*) or 0.01 ppm of formaldehyde in artificial smog (*206*). Formaldehyde causes skin irritation in guinea pigs (*39*) and in humans (*87, 186*).

The NAS report "Formaldehyde and Other Aldehydes" (*170*) mentions various effects of formaldehyde on the central nervous system in humans. For example, CNS effects such as thirst, dizziness and apathy, and inability to concentrate have been reported in workers using formaldehyde resin (*169*). Electroencephalographic (EEG) changes have been reported in human subjects exposed to 0.044 ppm of formaldehyde (*71*).

Formaldehyde causes hyperemia or inflammation in liver and kidney in rats (*71, 73, 88, 216*). Microscopically, formaldehyde also causes cloudy swelling, cytoplasmic vacuolization, and necrosis in the liver, and hyperemia, edema, and necrosis in the kidney. Macroscopic changes in the liver have also been produced by formaldehyde. When exposure is repeated over a period of weeks, changes include a mottled appearance and a decrease in liver weight (*13, 77*). Following a single high exposure, liver size may increase (*201*). Similarly, Murphy *et al.* (*167*) found that liver weight (absolute and relative to body weight) increased in rats following a single inhalation exposure to 35 ppm of formaldehyde for 18 h.

The toxic effects on liver that occur in response to high levels of exposure are usually more pronounced and occur more frequently than those caused by lower levels (*13, 73, 77*). Consequently, a general dose–response relationship may exist for organ toxicity caused by formaldehyde. For example, in the study conducted for CIIT, inhalation of formaldehyde caused changes in liver weight as well as microscopic changes in the livers of mice at 14.3 ppm, but caused only significant decreases in relative liver weights at 6 ppm in mice (*13*). Similarly, in the Formaldehyde Institute study, inhalation of 3 ppm of formaldehyde caused a decrease only in liver weight (*77*). At 6 and 12 months, in the CIIT study, hepatic centrilobular vacuolization and necrosis occurred in mice receiving 14.3 ppm but not in the control groups (p <0.001) (*13*). Similar changes occurred in rats that inhaled 0.8 ppm of formaldehyde in a reproductive study (*88, 89*). An abstract of one study reported that dermally applied formaldehyde caused liver changes (*208*).

Transient effects on the hematopoietic system occurred in rats and mice after 6 months of exposure to formaldehyde by inhalation (*13*). These effects were reflected by statistically significant decreases in (1) reticulocytes in female mice exposed to 2.1, 5.6, or 14.3 ppm; (2) mean corpuscular hemoglobin in male and female rats exposed to 14.3 ppm of formaldehyde; and (3) mean corpuscular hemoglobin concentration in male rats exposed to 2.1, 5.6, or 14.3 ppm of HCHO (*13*). Male and female rats had significant ($p < 0.05$) increases in mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and myeloid to erythroid ratios after 13 weeks of exposure by inhalation to 12.7 ppm of formaldehyde (*163*). This could indicate myeloid hyperplasia or erythroid hypoplasia.

Microscopic examination of the tissues in this study (which involved three exposure concentrations: 4.0, 12.7, and 38.6 ppm) revealed several lesions that resulted from exposure to 38.6 ppm of formaldehyde (*163*). In rats, the lesions included ulceration and necrosis of the nasal turbinates and trachea, congestion and hemorrhage in the lungs, congestion of hepatic sinusoids, and cytoplasmic vacuolation and congestion of the adrenal cortex. Some of these microscopic changes could have resulted from secondary effects of formaldehyde. Formaldehyde-related changes in mice included necrosis of the nasal turbinates and trachea, and pulmonary congestion and hemorrhage.

The effects of subchronic exposure to formaldehyde have also been examined in a study in which mice were exposed to formaldehyde by inhalation (*139*). Five groups of 10 male and 10 female mice each were exposed for 6 h/day, 5 days/week for 13 weeks to concentrations of either 2, 4, 10, 20, or 40 ppm of formaldehyde. Although the study was designed only to help establish exposure levels for a subsequent chronic toxicity study, which was never done, it produced some interesting findings. At 4 ppm and above, a dose-related increase in squamous metaplasia of the nasal cavity developed. At 10 ppm and above, epithelial hyperplasia, squamous metaplasia, and inflammation of the trachea also developed. In addition to these changes, at 40 ppm bronchial inflammation, epithelial hyperplasia, metaplasia, and granulation were observed. There was also an 80%

mortality rate at 40 ppm. The study revealed a significant depression of weight in both sexes at 20 and 40 ppm.

Interestingly, a few systemic effects at 40 ppm were sex related. These included ovarian involution and endometrial atrophy and a decrease in the liver to body weight ratio in female mice. These findings are particularly interesting because Shumilina (*214*) reported that several menstrual and reproductive alterations occurred in women who were exposed to formaldehyde during their work. (Details of Shumilina's findings are presented in Section XI.) Both sexes showed atrophy and necrosis of the thymus.

This study shows that 65 days of exposure to formaldehyde with weekly recovery periods of 48 h will produce significant changes in the upper respiratory tract at 4.0 ppm and serious systemic effects and death at 40 ppm (*13*).

In a study conducted for Biodynamics, the subchronic toxicity of formaldehyde was studied under contract by the Synthetic Organic Chemical Manufacturers' Association (*77*). They exposed rats, hamsters, and monkeys to concentrations of 0.2, 1.0, or 3.0 ppm for 22 h a day, 7 days a week, for 26 weeks. The summary table of microscopic findings in rats exposed to 0.2 or 1.0 ppm of formaldehyde revealed that albuminous degeneration of hepatocytes, hyperplasia of the bile duct, and focal hemorrhage developed in the livers of several of them. These changes did not occur in the concurrent control group. Four of the five rats exposed to 1.0 ppm and whose organs were subjected to microscopic examination also had hepatic necrosis. The necrosis did not occur in the other groups. At 3.0 ppm, the liver weight and the liver to body weight ratio were significantly decreased in rats, but necrosis of the liver was not seen.

VII. HYPERSENSITIZATION

Formaldehyde solution and probably gas, as well as polymers containing formaldehyde, have induced and elicited hypersensitivity reactions in humans. Dermal reactions may follow dermal or inhalation exposure and may be immediate or delayed in nature. Immediate reactions are characterized by urticaria, while the more common delayed reactions lead to erythema, edema, and vesiculation. Respiratory reactions result from exposure to airborne formaldehyde and are characterized by rhinitis or asthma. Asthmatic responses may be immediate or late, with present data indicating that at least late reactions to formaldehyde are of immunologic origin.

Early work by Horsfall (*112*) demonstrated that formaldehyde produced delayed contact dermatitis in a sensitive patient when tested by immersion of the hand in formaldehyde solution as low as 0.2 ppm. When the patient inhaled formaldehyde through a mouthpiece, a delayed dermal reaction was also produced. Rostenberg *et al.* (*197*) confirmed Horsfall's finding that formaldehyde could cause a delayed contact dermatitis. These investigators studied nurses who developed dermatitis from repeatedly handling thermometers sterilized in 10% formaldehyde. Positive reactions were elicited by patch tests with 0.5% formaldehyde. More recent studies involving dermatologic patients from many countries, including the United States, have shown that 1–7% of these patients were sensitive to 2% formaldehyde by patch testing (*34, 47, 81, 105, 198, 199, 222*). Approximately 5–8% of subjects without dermatologic complaints (selected from the San Francisco area) became sensitized following dermal exposure to formaldehyde in concentrations of 0.37–3.7% and challenge concentrations of 0.3% (*154*). Later work by Jordan (*125*) showed that positive delayed reactions were found to occur in dermatologic patients by patch testing with 30 ppm of formaldehyde (four of nine patients). However, spraying 28 ppm of formaldehyde in water on exposed skin did not produce a positive reaction.

Positive dermal sensitization reactions to formaldehyde have been caused by many products including textiles (*17, 47, 114*), paper (*20, 75*), cleaning agents (*80, 132*), coolants (*10, 96*), nail hardeners (*47, 162, 183*), photographic chemicals (*47, 75*), and embalming fluid (*47*). Delayed contact dermatitis reactions have also been produced by resins containing formaldehyde. These include melamine–formaldehyde (*79, 146b, 146c*), urea–formaldehyde (*111*), and phenol–formaldehyde resins (*47, 49, 78, 149, 150*). Immediate dermal reactions to formaldehyde or products containing formaldehyde have also been reported (*74, 106, 125, 156*).

Exposure to formaldehyde vapor has produced rhinitis in exposed individuals (*205, 240*), as well as bronchial asthma (*3, 14, 108, 174, 188*). The development of bronchial asthma following exposure to formaldehyde vapor is perhaps best demonstrated by the study of Hendrick and Lane (*108*). They included five staff members of a hemodialysis unit, two of whom developed wheezing, chest tightness, and cough after several months of repeated exposure to formaldehyde. Symptoms were delayed and worsened at night. Various hematological changes including eosinophilia were also noted. Provocative inhalation tests, in which either 25 or 10% formalin was painted on a board in a chamber, produced similar late asthmatic symptoms in these individuals. Later work (*109*) showed that formaldehyde concentrations during these exposures approximated 5 and 3 ppm, respectively. The several-month exposure period required for development of symptoms, the delayed onset and recurrent nocturnal pattern of the asthma, and the development of eosinophilia are all consistent with an immunological reaction as opposed to an irritation reaction. A late asthmatic reaction has also been reported (*3*) to occur in a painter who was exposed to 2 ppm of formaldehyde in a provocative inhalation test. This individual initially experienced rhinitis and then asthma while spraying paint later found to contain formaldehyde.

Inhaled formaldehyde vapor can also produce an immediate reaction in exposed individuals (*14*). In another case, Frigas *et al.* (*82*) reported an immediate response following provocative inhalation tests with pulverized urea–formaldehyde foam insulation: the response did not occur with formaldehyde gas delivered through a face mask. Aluminum oxide dust did not produce a reaction in this patient who had developed asthma following insulation of her house with urea–formaldehyde foam insulation. The immunological nature of the immediate reactions is more open to question since IgE antibodies have not been isolated from exposed humans as they have in some cases for other chemical allergens such as isocyanates (*16*) and trimellitic anhydride (*184*). Demonstration of asthmatic responses at low formaldehyde exposures may depend upon the presence of particulates. Respiratory symptoms have also developed in workers exposed to hexamethylenetetramine–resorcinol (HR) resin (*84*). More recently, work by Frigas *et al.* (*82*) has shown that 37 other individuals with respiratory symptoms, following formaldehyde exposure at home or on the job, did not develop asthma following inhalation of formaldehyde gas in compressed breathing air. Since previous investigators (*3, 108, 188*) used room air rather than compressed breathing air, the presence of naturally occurring particulates in the room air used by these previous investigators may have allowed formaldehyde to penetrate into the lungs. It is known that particulates aid formaldehyde in reaching the lower respiratory tract (*5, 6, 139*).

VIII. TERATOGENIC AND REPRODUCTIVE EFFECTS

The potential of formaldehyde to interfere with embryonic and fetal development has been reviewed previously (*70*). Since then, studies on the toxicity of formaldehyde have been completed that provide additional information about the reproductive and teratogenic effects of this chemical. This section discusses the main findings of the earlier studies and relates them to the results of more recent research.

A. Inhalation Studies

In a series of four publications beginning in 1968, Gofmekler and colleagues reported on the toxic and teratogenic effects of formaldehyde (*88–90, 191*). All of these publications appear to be based on an experiment in which 36 female rats (12 per group) were exposed to 0, 0.01, or 0.83 ppm of formaldehyde from 10 to 14 days before impregnation through gestation. Three male rats per dose level were also exposed for 6 to 10 days before mating.

In 1968, Gofmekler (*88*) reported the effects of formaldehyde on fertility, fetal weights, and organ weights. At 0.01 and 0.83 ppm, formaldehyde increased the duration of gestation by 14–15% as well as the average body weight of offspring and their heart, adrenal, and kidney weights. In contrast, the liver and lungs from pups in the treated groups weighed less than those from the control pups. This finding likely represents direct or indirect effects of formaldehyde on developing fetal lung and liver. Although Gofmekler reported a decrease in the litter size, data in the article show that exposed groups had average litter sizes of 19.6 and 17.3 pups, as compared to the control value of 11.2, which is nearer a "normal" size. For these calculations, Gofmekler apparently assumed that all females in each group became pregnant.

Gofmekler *et al.* (*89*) published additional results related to the effects of HCHO (0.01 and 0.83 ppm) on the developing embryo [identical data were reported by Pushkina *et al.* (*191*)]. Significant decreases in ascorbic acid concentrations occurred in the whole embryo and in the maternal liver at both dose levels. A significant increase in the ascorbic acid concentration in liver occurred in offspring from dams exposed to 0.01 ppm only. The lack of a similar change in the group exposed to 0.83 ppm, however, raises questions about the significance of this finding. RNA concentrations in maternal livers were greater at both dose levels than they were in controls. RNA concentrations of fetal brain were similar in control and treated groups. DNA content was significantly lower in maternal and fetal liver in both treated groups and control animals. The authors concluded that formaldehyde "significantly inhibited the synthesis of nucleic acids." However, because the RNA concentration in the liver increased as the DNA concentration decreased, this conclusion is not completely supported by the data in the article.

The above publication (*89*) also describes microscopic changes in the liver, kidneys, and other organs of fetuses from dams exposed to 0.01 or 0.83 ppm of formaldehyde. Changes in the liver included an increased proliferation of epithelial cells in the bile duct and segmented forms in the hepatic sinusoids. Changes in the kidney included renal epithelial cells with polymorphic nuclei, casts in the lumina of some tubules, and functional alterations in the renal tubule apparatus. Also, exposure to 0.83 ppm decreased myocardial glycogen, involuted thymic lymphoid tissue, and disintegrated lymphocytes. Histologically, the testes of adult males exposed to formaldehyde were similar to those of the controls. In contrast, formaldehyde inhalation by pregnant dams did not cause macroscopically discernible changes in embryonic or fetal development; there were no terata.

Sheveleva (*211*) studied the teratogenic potential of formaldehyde in pregnant albino rats. The dams were exposed by inhalation to 0.004, 0.0004, or 0.0 ppm of formaldehyde for 4 h each day on days 1 through 19 of gestation. Fifteen females per group were killed on day 20, while six were kept to obtain progeny. Exposure to 0.004 ppm of formaldehyde decreased neuromuscular excitability, spontaneous mobility, rectal temperature, and hemoglobin concentration in the dams.

On day 20, the number of preimplantation deaths was higher in both groups exposed to formaldehyde than it was in the controls. The number of live fetuses was approximately the same in all groups. If added together, these data indicate that the number of zygotes was *greater* in dams that were exposed to formaldehyde. If that is correct, the data provide indirect support for the findings of Gofmekler (*88*) showing an increase in litter size. Until more research is done, the potential effect of HCHO on litter size will remain uncertain. In Sheveleva's study, no external malformations were observed in the offspring that were removed by hysterotomy. This finding is similar to that of Gofmekler and his colleagues (*88, 89*) as well as other researchers (*152, 179, 180*).

On day 22, six dams from each group delivered offspring; all progeny appeared to be normal at birth (*211*). At 1 month postnatal, the female offspring from control dams were larger than the female offspring from treated dams. For male progeny, the opposite was true. At 1 month, the spontaneous mobility of progeny from treated dams was less than that of control progeny. By 2 months, the hemoglobin and leukocyte concentrations were decreased in progeny of dams exposed to formaldehyde, but not in a dose-related manner (*211*).

Guseva (*95*) measured the nucleic acid content in the testes of rats exposed to formaldehyde. During a 6-month exposure period, three groups of male rats received formaldehyde orally and by inhalation as follows: Group 1, 0.1 mg/liter in drinking water and 0.4 ppm by inhalation; Group 2, 0.01 mg/liter in drinking water and 0.2 ppm by inhalation; Group 3, 0.005 mg/liter in drinking water and 0.1 ppm by inhalation. Group 4 served as untreated controls. Exposure in the drinking water was continuous. Simultaneous exposure to formaldehyde by both routes occurred five times per week for 4 h each time. Reproductive function was evaluated by pairing each treated male with two virgin untreated females and evaluating the resulting pregnancies. On day 20, an unspecified number of pregnant females were killed and their offspring were removed and examined. The remaining dams were allowed to produce offspring. Guseva did not report the results of the examination of the fetuses. The number and weight of newborn rats were recorded. Observations of their subsequent development extended over 1 month. The time of eye opening and other developmental indices were recorded for the offspring of males in Groups 1 and 3 only.

There was no effect of formaldehyde on the weight of the fetuses or the size of the litters. The offspring were morphologically normal at birth and developed normally thereafter. Gonadotropin levels were not significantly different between males in the control group and those in the treatment groups. However, the amount of nucleic acid in the testes of males exposed to 0.4 and 0.2 ppm of formaldehyde was significantly less than the amount in the testes of the controls (*95*).

Sanotskii *et al.* (*202*) studied the effects of formaldehyde on reproduction in an unspecified strain and number of albino rats. They exposed groups of pregnant and nonpregnant rats to 0, 0.4, or 0.5 ppm of formaldehyde for 4 h per day for 20 days. Nonpregnant rats responded more to the effects of formaldehyde than did pregnant ones. In nonpregnant rats, exposure to formaldehyde at 5.0 ppm altered renal function by decreasing daily diuresis and urinary chlorides, and increasing urinary protein concentrations. The increase in concentration of protein in urine may have simply reflected decreased urinary output. Altered hepatic function was manifested by a decrease in urinary excretion of hippuric acid. At 5 ppm only, blood hemoglobin decreased in the pregnant rats. This finding supports the findings by CIIT that exposure to 2 ppm of formaldehyde and above in rats decreases mean corpuscular volume and mean corpuscular hemoglobin concentration after 6 months of exposure (*13*). Exposure to 0.4 ppm did not affect the parameters that were estimated for either pregnant or nonpregnant rats.

B. Dermal Studies

We found one teratology study of formaldehyde in which exposure was by dermal application. In a pilot study, Overman (*179*) applied formalin to the denuded back of pregnant hamsters for 2 h per day on days 7–11 of gestation. This treatment resulted in a potentially meaningful increase in resorptions and birth defects. To determine if the changes were significant, he repeated the study using larger numbers of animals. In this latter study, exposure to HCHO did not affect the survival or development of the offspring of hamsters (*180*).

C. Ingestion Studies

Although human exposure to formaldehyde occurs most commonly by the respiratory and dermal routes, it may occur by the ingestion of formaldehyde-based preservatives. One teratogenic study of HCHO following oral ingestion has been done. Marks *et al.* (*152*) intubated pregnant albino mice on days 6–15 of gestation with 0, 74, 148, or 185 mg/kg/day. On day 19, the mice were killed and the offspring were examined. At 185 mg/kg, HCHO was toxic to 22 of 34 pregnant mice. At 74 mg/kg, there was a significant decrease in average weight gain during pregnancy. Treatment with HCHO did not result in malformed offspring. Because formaldehyde reacts with or binds to chyme and intestinal contents, as well as to tissue, the amount of HCHO that test animals are exposed to following ingestion is unknown.

Hexamethylenetetramine (HMT), an antimicrobial food additive as well as a medication used to treat chronic bladder infections, degrades to formaldehyde and ammonia in an acid medium or in the presence of protein (*93*). Reproductive studies using orally administered HMT have produced information that helps us to understand the potential effects of formaldehyde.

In 1970, Della Porta *et al.* (*55*) reported on the effects of orally administered HMT in rats. Females and males were given 1% HMT in the drinking water, beginning when the rats were 8 weeks old. Two weeks later, the animals were mated, and treatment of the females was continued during pregnancy and nursing. A group of 24 male and 24 female progeny was randomly selected for continued exposure to HCHO until they were 20 weeks old. Groups of 12 untreated dams and 48 pups were used as controls.

Treated females and control females produced 124 and 118 offspring, respectively. The progeny of the treated dams were not malformed although mean body weights of the treated males and females were significantly less than those of controls. The weights remained depressed for up to 9 weeks for males and up to 13 weeks for females before becoming comparable to those of the controls. When the offspring were autopsied at 22 weeks, no macroscopic or microscopic lesions were seen. Body weights and organ weights (liver, kidneys, spleen, thymus, pituitary, adrenals, and testes) of offspring were similar for treated and control groups.

A second experiment reported in this article involved exposure of rats to HMT in the drinking water over three generations. F_1 and F_2 animals were given HMT until week 40 postnatal; F_3 animals were given HMT until week 20. F_1, F_2, and F_3 animals were observed for 130 weeks; survivors were sacrificed at 3 years of age. The survival rates of all the generations of offspring were not affected by HCHO. Mean body weights obtained during the experiments showed no significant differences between control and treated groups.

One year later, Natvig *et al.* (*171*) reported findings similar to those of Della Porta *et al.* (*55*) when they gave HMT in the feed to Wistar rats. Male and female rats were fed a diet containing either 0.0 or 0.16% HMT starting at 2 months of age and continuing for 3 months, then mated with group mates. Their offspring were fed the same diet. The offspring were weighed at 7 and 15 weeks, measured for voluntary muscle activity at 6 weeks, and killed when they were 123 days old. There were no detectable differences between rats in the test and control groups. The fertility of the treated animals was similar to that of control animals. The offspring from both groups had similar muscular activity, body weights, general health, and organ weights.

Formaldehyde administered in the diet had no effect on reproduction in beagles (*116*). From 4 days after mating to day 56 of pregnancy, pregnant bitches were fed concentrations of 600 or 1250 ppm HMT, or of 125 or 375 ppm formaldehyde in the diet. Control dogs ate unadulterated chow. Neither formaldehyde nor HMT affected the pregnancy rate. Maternal body weights increased normally during pregnancy in all groups. The duration of gestation was not affected by formaldehyde or HMT. Mean litter sizes were within the normal range for all groups. The group that received 1250 ppm of HMT had a greater percentage of stillborn pups than any other group; this was due mainly to one litter in which seven of nine pups were dead. The stillborn pups were not malformed. At 1250 ppm of HMT, there were some signs of neonatal toxicity.

During the first month after parturition, the pups from bitches given 1250 ppm HMT grew less than normal. The retarded growth coincided with increased neonatal mortality. Consequently, the percentage of pups that survived to weaning was lower than it was in the other groups. Nevertheless, pups that survived for up to 9 months exhibited normal behavior, appearance, mobility, and muscular coordination.

D. Injection Studies

Palkovits and Mitro (*182*) studied formalin-induced stress in neonatal rats. They injected one group of newborn Wistar rats with 0.02 ml of 2% formaldehyde ip once on the day of birth. A second group was injected daily for the first 4 days after birth. Control animals were untreated. All neonates were decapitated 24 h after the last injections.

In the neonates injected for 4 days, degenerative cellular atrophy occurred in the ventromedial arcuate of the hypothalamus. Single injections of formaldehyde did not cause degenerative changes but did cause decreased cellular activity in the medial field of the ventromedial nucleus and in the arcuate nucleus and an accumulation of granules in the neuronal cytoplasm. In both groups, formaldehyde injections increased nuclear volume in the adrenals. These changes indicate that the hypothalamus of the neonatal rat is sensitive to corticoid feedback induced by formaldehyde administration.

Cohen (*38*) studied the response to formaldehyde injection of fetal rats by measuring ascorbic acid levels in the adrenals. The first fetus from each litter served as the control. During a hysterotomy, approximately 6 μl/g body weight of 2% formaldehyde was injected sc into one or more litter mates. Fetuses were injected with formaldehyde at either 18.5, 19.5, 20.5, or 21.5 days of gestation. Injections of formaldehyde at 20.5 days of gestation resulted in decreased ascorbic acid levels in the adrenals. Injections on other days of gestation did not cause this response in fetuses.

Conner *et al.* (*42*) studied the contragestational properties of formaldehyde. On day 3 or 7 after mating, 0.05 ml of 40, 20, 10, 7, 3.5, 2.0, 0.5, 0.05, or 0.0005% formaldehyde was instilled into one uterine horn and 0.09% saline into the other horn (control) of pregnant Sprague–Dawley rats. All solutions of formaldehyde also contained 12–15% methanol. On day 15, dams were sacrificed.

Injections of 40 and 20% formaldehyde produced maternal toxicity and death. Injections of 7.0 through 0.5% on day 3 terminated most pregnancies. When these concentrations were injected on day 7, most pregnancies continued. The authors concluded that the contragestational properties of formaldehyde were similar to those of other protein denaturing agents, including ethanol, methanol, and silver nitrate. Because methanol solutions alone were not tested, contragestational effects of methanol could not be clearly distinguished from those of formaldehyde.

E. *In Vitro* Studies

Johnson (*122*) used an *in vitro* assay involving hydra to evaluate the teratogenic potential of formaldehyde. The minimal concentration of formaldehyde that was toxic to the adult hydra was also teratogenic. More importantly, the maximal concentration of formaldehyde that was not toxic to the adult hydra was also not teratogenic. This *in vitro* assay system with hydra has been used to evaluate numerous chemicals (*123*). It accurately predicts the ratio of teratogenic doses to maternally toxic doses for several mammalian species *in vivo*. From the results of this assay, a chemical would probably not be expected to cause terata at an exposure that was not also toxic to the adult. Such a prediction is consistent with results of *in vivo* assays (*152, 180*).

IX. GENETIC EFFECTS

Formaldehyde has been found to be mutagenic to viruses, *Escherichia coli, Pseudomonas fluorescens, Salmonella typhimurium*, and to strains of yeast, fungi, *Drosophila*, grasshopper, and mammalian cells (*11, 70, 117, 225*). It produces gene mutations and chromosomal aberrations, including deficiencies, duplications, inversions, and translocations. In most experiments, although the results were positive, dose–response relationships were difficult to demonstrate (*70*). In the presence of other mutagens, such as X rays, ultraviolet radiation, and hydrogen peroxide, formaldehyde increases the frequencies of observed mutants. In *E. coli* and *Saccharomyces cerevisiae*, the lethal and mutagenic effects of formaldehyde are greater in the test systems using excision repair-deficient strains than in those with normal repair mechanisms (*69*). The mutations or DNA damage caused by formaldehyde may be related to its ability to cause crosslinks in nucleic acids (*36*).

The recent work of Temcharoen and Thilly (*225*) showed a positive relationship between the time and concentration of formaldehyde exposure and the mutagenic and toxic effects observed in *S. typhimurium* (strain TM 677) *in vitro*, both with and without rat liver microsomes. Connor *et al.* (*43*) recently found positive results using formalin in the Ames assay, thus confirming the mutagenic effects of formaldehyde. They also found the mutagenicity expressed over a narrow range of exposure concentrations.

In vivo assays using mammalian cells showed that formaldehyde induces sister-chromatid exchange in hamster ovary cells and in human lymphocytes (*175*). Formaldehyde also causes cell transformation in the mouse BALB/c 3T3 cells (*117*). Brusick (*32*) used the BALB/c 3T3 cell to demonstrate that formaldehyde acts as both an initiator and a promoter of cell transformation. Other data indicate that formaldehyde can initiate C3H/10T1/2 cell transformation with tetradecanoylphorbol acetate (TPA) as a promoter and that formaldehyde can act as a promoter in C3H/10T1/2 cells initiated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (*26*).

Whole animal systems have been used to evaluate the mutagenic potential of formaldehyde. It caused chromosome breaks in the spermatocytes of the grasshopper (*151*) and mutations in early larval spermatocytes of *Drosophila melanogaster* (*11*). Formaldehyde did not induce dominant lethal mutations in mice (*66*). More recently, Fontignie-Houbrechts (*76*) reported increased dominant lethality during weeks 1 and 3 after treatments of male mice with 50 mg/kg (ip) of formaldehyde; the effect was marginal, however, and may not have been treatment related. At all matings in this study, treated and control dams averaged less than 1.0 resorption each. To reveal statistical differences between control and treatment groups, preimplantation losses were added to postimplantation losses. The accurate determination of preimplantation losses, however, depends upon an accurate counting of corpora lutea, which is difficult and subject to a 10–15% error.

Data are becoming available that demonstrate that formaldehyde induces mutagenic changes in human cells *in vitro* and possibly in humans themselves. Goldmacher and Thilly (*91*) grew lymphoblast TK6 cells from a human donor *in vitro* and exposed them to formaldehyde for 2 h. At 4.6 ppm (150 μM), formaldehyde induced a significant number of mutations in the cells. The minimal concentration of formaldehyde that induced a detectable number of mutations was 4.0 ppm. Between 4.0 and 4.6 ppm, there seemed to be a simple linear dose–response relationship between the concentration of formaldehyde used and the number of mutations induced. Data on other chemicals that have been tested using the same system indicate that a simple linear dose–response relation should exist for formaldehyde at even lower concentrations. Thus, according to the authors, 10 exposures at 0.2 ppm would probably cause a mutagenic response of similar magnitude to that caused by 1 exposure at 2.0 ppm.

Evidence is beginning to appear showing that chromosomal effects observed *in vitro* following formaldehyde exposure could also occur in human leukocytes *in vivo*. Preliminary data were recently obtained on eight medical students who were exposed intermittently to about 1.0 ppm of formaldehyde during a 10-week anatomy course (*221*). As compared with control students, the students who were exposed to formaldehyde had an increase in sister-chromatid exchange rates in the chromosomes. If additional research validates these preliminary data, the findings could provide important insight into the potential chromosomal effects of formaldehyde on humans.

X. CARCINOGENICITY

Over the past 30 years, numerous animal studies have been reported in the literature concerning the carcinogenicity of formaldehyde. These include studies conducted with rats (*4, 13, 56, 242, 243*), mice (*13, 56, 113*), hamsters (*51*), and rabbits (*166*) by various exposure routes. With the exception of a few recent studies (*4, 13*), the interpretation of earlier studies is complicated by a variety of limitations relating to the extent of histopathology, dose, duration, number of animals tested and survived, lack of controls, route of administration, and chemical form tested.

By far the two most important carcinogenesis studies conducted to date with formaldehyde are the recently completed Chemical Industry Institute of Toxicology study (*13*) and the New York University (NYU) study reported by Albert *et al.* (*4*).

In the recent CIIT study (*13*), F344 rats and $B6C3F_1$ mice were exposed by inhalation to 0, 2, 5.6, or 14.3 ppm of formaldehyde for 6 h/day, 5 days/week for up to 2 years. Initially, 240 animals (120 males and 120 females) were exposed at each level. Randomly selected animals were sacrificed at 6, 12, 18, and 24 months. Additional rats from each group were also sacrificed at 27 or 30 months of the experiment. Over 50% of the rats exposed to 14.3 ppm of formaldehyde experienced an early unscheduled death, many due to squamous cell carcinoma of the nasal cavity, whereas in other exposure groups proportions of unscheduled early deaths ranged from 13 to 22% of the total number of rats exposed. Approximately 40 tissues were evaluated histopathologically from all animals except the 2- and 5.6-ppm animals sacrificed at 6 and 12 months. All gross lesions were histopathologically examined, and, for the nasal cavity examinations, multiple sections were evaluated.

At about month 12 of the study, the first nasal cancer was noted in a rat exposed to 14.3 ppm formaldehyde. By month 18, it was reported that 37 rats exposed to 14.3 ppm of formaldehyde had nasal cancer: 28 squamous cell carcinomas and 1 spindle cell sarcoma among 44 rats dead or moribund, and 8 squamous cell carcinomas among 40 rats sacrificed at 18 months (*224*). Other dose-related changes observed in rats at this time were squamous metaplasia and dysplasia of the nasal mucosa. After 24 months of exposure, the number of rats with nasal cancers at 14.3 ppm increased to 108: 103 squamous cell carcinoma, 2 nasal carcinoma, 2 undifferentiated carcinoma or sarcoma, 1 carcinosarcoma. Of the rats exposed to 5.6 ppm, two had squamous cell carcinoma of the nasal cavity. Tracheal metaplasia and bone marrow hyperplasia were also observed in rats exposed to 14.3 ppm. In addition, in all three formaldehyde-exposed groups, polypoid adenomas in the nasal cavity were observed. The incidence of the adenomas among animals that survived until 24 months appeared to increase in a dose-related manner (*13*).

In mice, squamous cell carcinoma occurred in the nasal cavities of two males at 14.3 ppm formaldehyde exposure in the CIIT study. In addition, a significant increase in the incidences of some of the nonneoplastic lesions (epithelial dysplasia, squamous cell metaplasia) was observed in mice exposed to 5.6 or 14.3 ppm formaldehyde. Mortality was substantial in all groups of male mice, but this was primarily attributed to fighting for dominance among the group-caged male mice. Wounds inflicted by cage mates resulted in infection and subsequent death.

In light of the extremely low spontaneous incidence rate of this type of cancer (*235*), and the high incidence of the same type of cancer in rats exposed to formaldehyde, the nasal cancers in mice are believed to be related to formaldehyde exposure. It should be noted that mice were able to decrease their rate and volume of respiration such that the dose of formaldehyde received by mice at 15 ppm was approximately equivalent to that received by rats at 5.6 ppm (*12*). Thus the carcinogenic response of these two species may be very similar.

The CIIT study protocol and sections of nasal cavities and other tissues from exposed and control rats sacrificed at 6, 12, and 18 months of the study were reviewed by a panel of pathologists formed by the Interagency Regulatory Liaison Group (*25*). All tissues of exposed (14.3 ppm) and control mice sacrificed at 6 and 12 months also were examined by the panel. The members of the panel generally concurred with the observations, diagnoses, and interpretations of the CIIT pathologists (*25*). It was found, after histopathological analysis of the nasal cavities of formaldehyde-exposed animals, that no ulceration occurred in the nasal cavities at 6 or more months.

The methodology for formaldehyde generation and measurement was also reviewed by a panel of experts, which agreed that "the Battelle approach to formaldehyde vapor generation was a suitable adoption of accepted methods and principles and, therefore, it was sound and based upon the best available technology. The same type of assessment applied to the chamber air monitoring system, which also combined two well-established procedures" (*94*).

Two experiments conducted at NYU produced findings similar to those reported by CIIT (*4*). In the first experiment, 99 male Sprague–Dawley rats were exposed to a mixture of formaldehyde and hydrogen chloride (HCl) at concentrations of 14.7 and 10.6 ppm, respectively, for 6 h/day, 5 days/week for life. Groups of 50 air sham-exposed and 50 untreated rats were used as controls. Histologic sections were taken from the nasal cavity, larynx, trachea, pulmonary lobes, liver, bladder, kidney, spleen, and other organs with gross pathologic alterations. Bis(chloromethyl) ether (BCME) levels in the exposure chamber were too low to measure but were estimated to average about 1.0 ppb. Of the 99 rats exposed to the gaseous formaldehyde and hydrogen chloride, 28 developed nasal tumors: 25 squamous cell carcinomas and 3 papillomas. The first carcinoma was seen at 223 days. No tumors were observed in the respiratory tract of the controls.

Formaldehyde and HCl can combine to form BCME. BCME can cause lung and nasal cancer in rats upon inhalation. The most common type of nasal cancer induced by BCME in rats was esthesioneuroepithelioma (a tumor of the nerve tissue) and not squamous cell carcinoma as actually observed (*138*, *142*). It was unlikely that BCME was involved in the development of the nasal cancer observed in this experiment because (1) it normally induces esthesioneuroepithelioma and (2) its concentration in the exposure chamber (1.0 ppb) was estimated to be far below that which previously produced carcinoma in rats. This experiment appears to support the findings of the CIIT study but was complicated by the presence of minute amounts of BCME and by the unknown effects of HCl alone or in combination with appropriate control groups.

In the second experiment, 100 male Sprague–Dawley rats were used in each of the following exposure groups: (1) gaseous mixture group as in Experiment I; (2) combined exposure to HCHO and HCl, in which the two gases were not premixed at high concentrations but fed separately into the inlet air supply of the exposure chamber; (3) formaldehyde alone; (4) hydrogen chloride alone; and (5) air sham-exposed controls. Formaldehyde concentrations ranged from 14.1 to 14.3 ppm, while HCl concentrations in groups ranged from 9.5 to 10.2 ppm. No BCME measurements had been made at the time of the reporting. The experiment had been in progress for 588 days at the time of the report. Therefore, the tumor data reported include only nasal lesions in rats that produced grossly evident nasal swelling. The number of nasal cancers in each group is as follows: Group 1, 12; Group 2, 6; Group 3, 10; Group 4, 0; Group 5, 0. Final results are yet to be reported. A significantly greater degree of irritation was observed in rats exposed to formaldehyde plus HCl as opposed to rats exposed to formaldehyde alone.

The results of the CIIT and the NYU studies provide adequate evidence that formaldehyde gas is carcinogenic in two strains of rats. In addition, formaldehyde appears to have induced nasal cancer in $B6C3F_1$ mice.

The carcinogenic potential of formaldehyde was tested also in hamsters and mice in combination with the known chemical carcinogens diethylnitrosamine (*51*) and coal tar (*113*). Dalbey (*51*) studied the potential carcinogenicity of formaldehyde and the possible tumor-promoting activity of formaldehyde in hamsters. In the first experiment, male Syrian golden hamsters were exposed to

10 ppm formaldehyde for 5 h/day, 5 days/week for life. Histopathologic examinations were made on two sections of the nasal turbinates, larynx, trachea, and lung; nasal sections were not consistently cut. No tumors were observed in histologic sections of respiratory tract tissues in either control or treated animals. Both hyperplastic and metaplastic areas were observed in the nasal epithelium of 5% of the hamsters exposed to formaldehyde, whereas none was observed in control animals. Survival in both treated and control groups was very poor: over 40% of the animals died within 80 weeks of the study, and over 80% of the animals died within 100 weeks.

The second experiment involved groups of male Syrian golden hamsters. The first group was exposed to 20 ppm formaldehyde for 5 h/day, 1 day/week for life. The second group received injections of 0.5 mg of diethylnitrosamine (DEN) once weekly for 10 weeks. The third group was exposed to 30 ppm formaldehyde 48 h prior to each of 10 weekly DEN injections, followed by weekly HCHO exposures for lifetime, but beginning 2 weeks after the last DEN injection. Survival of hamsters in all groups was again poor: over 40% of the animals died within 60 weeks of the study. No tumors were observed in untreated animals or in those receiving only formaldehyde. Tumors in one or more sites in the respiratory tract were observed in 77% of DEN-treated controls. Lifetime exposure to formaldehyde either prior to or after DEN injection did not significantly increase the number of tumor-bearing animals (TBA) above those DEN-only controls. However, the ratio of the number of tracheal tumors/TBA was almost doubled in the group given formaldehyde prior to each DEN injection over DEN-only controls. The author suggests that under these experimental conditions formaldehyde may enhance the carcinogenicity of DEN in the respiratory tract.

In the study reported by Horton *et al.* (*113*), groups of 42–60 C3H mice were exposed to coal tar aerosol and/or formaldehyde at concentrations of 40, 80, and 160 ppm for three 1-hour periods/week for 35 weeks. The 160-ppm group was exposed for only 4 weeks because of toxicity. Mice that survived 35 weeks at 40 ppm were subsequently exposed to 122 ppm of formaldehyde for another 35 weeks. Survival after 1 year was poor in all groups. There is no mention of histopathological evaluation of nasal tissues, so presumably no grossly visible tumors were observed. Coal tar-exposed mice developed lung cancer. However, in formaldehyde-exposed mice, no tumors were reported in lungs and trachea. The major limitations of this study for assessing the carcinogenic potential of formaldehyde are that too few animals survived beyond 1 year, exposures were too short, and histopathology was not adequately reported.

The carcinogenic potential of formaldehyde has also been tested by a variety of other routes of exposure, including oral (*56*), subcutaneous injection (*242, 243*), application to the buccal mucosa (*166*), and skin painting (*135, 219*).

Because of the limitations in the study design and lack of detailed description of study protocols, these studies could not provide firm evidence regarding formaldehyde carcinogenicity in animals. Notwithstanding the limitations, some of the studies suggest that formaldehyde may be carcinogenic in tissues other than nasal epithelium and in other species. These studies are discussed below.

Hexamethylenetetramine (HMT) is a urinary tract antiseptic that owes its activity to formaldehyde. HMT decomposes *in vivo* to generate formaldehyde and ammonia. The following two studies utilized HMT and are relevant for the evaluation of the carcinogenic potential of formaldehyde.

Della Porta *et al.* (*56*) administered HMT to the drinking water of CTM, SWR, or C3Hf mice at 1.25–12.5 g/kg body weight/day for up to 60 weeks while Wistar rats received HMT at 1.5–2.5 g/kg body weight/day for 104 weeks. No treatment-related tumors were observed either in mice or in rats.

In the second experiment, Watanabe and Sugimoto (*243*) injected rats subcutaneously with 1–2 ml of a 9–40% solution of HMT once a week until tumors developed. Of the 20 treated rats, 8 developed tumors: 7 sarcomas at the site of injection and 1 adenoma. Subcutaneous injection of formic acid, a metabolite of formaldehyde, did not induce tumors. Watanabe *et al.* (*242*) also injected rats subcutaneously with 0.4% formalin (1 ml/week for 15 months). Of the 10 rats treated, 4 developed sarcomas: 2 in the skin of the injection site, 1 in the liver, and 1 in the peritoneal cavity. The studies indicate that subcutaneous injection of formalin and HMT induced tumors. However, it is not certain what role the repeated injury to the subcutaneous tissue may have played in the induction of the sarcomas, even though results of formic acid injection were negative.

The other study suggesting formaldehyde-induced tumors at the site of application was reported by Mueller *et al.* (*166*). Rabbits were fitted with oral cavity tanks designed to continuously expose the palate to 3% formalin with minimal mechanical irritation. Six rabbits were exposed to formalin, 4 rabbits were fitted with oral tanks that did not contain formalin, and 10 rabbits served as controls. Each exposure lasted to 90 min and was repeated five times per week for a period of 10 months. Animals were sacrificed at 1 month after the last exposure. Of six rabbits treated with formalin, two developed grossly visible leukoplakias that, according to the authors, showed histological features of carcinoma *in situ*. In animals that were fitted with tanks without formalin, no lesions were apparent.

Two skin initation/promotion studies in mice were reported recently. Krivanek *et al.* (*135*) tested formaldehyde for its ability to irritate and/or promote skin tumorigenesis in CD-1 female mice. No treatment-related nodules were observed. A similar study by Spangler and Ward (*219*) also produced negative results. Preliminary data from the first 48 weeks of an ongoing 78-week study with female Sencar mice show no treatment-related tumors. It should be noted that in both studies it is uncertain as to how much of the highly volatile formaldehyde applied to mouse skin is actually being absorbed, and how much could penetrate the stratum corneum to reach a target.

Since formaldehyde causes cancer in experimental animals, the question of mechanism becomes important. Formaldehyde most likely acts through a genotoxic mechanism, although its ability to act as a promoter may play a role in the expression of its carcinogenicity. The genotoxic properties of formaldehyde are clearly indicated by its mutagenicity in viruses, bacteria, insects, and cultured mammalian cells (including human cells); it can also initiate mammalian cell transformation. Swenberg *et al.* (*223*) reported that exposure to 6 or 15 ppm of formaldehyde (but not to 2 ppm) for 6 h/day for 3 days increased cell turnover in the nasal cavity of rats. The increased cell turnover observed may in turn increase the likelihood of DNA damage becoming fixed, thus leading to tumor development. To what extent, however, increased cell turnover occurs beyond this very brief period is unknown. It can be surmised that squamous cells are more resistant to the toxic effects of formaldehyde and thus would tend to be less likely to undergo increased turnover.

There is also evidence that formaldehyde can act as a promoting agent. As Dalbey (*51*) reported, exposure of hamsters to 30 ppm of formaldehyde 2 days prior to each of 10 weekly injections of a known carcinogen, DEN, resulted in an increased number of tracheal adenomas per tumor-bearing animal as compared to hamsters given DEN only, whereas no tumors were found in the group treated with only formaldehyde. Additionally, it has been shown that in cell transformation assays formaldehyde can promote cells initiated by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, and formaldehyde-initiated cells can be promoted by tetradecanoylphorbol acetate. Thus, formaldehyde may exert its carcinogenic effect by one mechanism or a combination of mechanisms.

Some suggest that the cellular response to formaldehyde irritation is the direct and necessary precursor to development of cancer of the nasal cavity. Studies, however, have shown that not all chemicals capable of inducing epithelial hyperplasia, a specific irritant effect, cause cancer. For example, in the NYU study reported by Albert *et al.* (*4*), formaldehyde with or without irritant hydrochloric acid vapor produced similar numbers of nasal cancers, although the degree of irritation with hydrochloric acid was greater than with formaldehyde alone. Furthermore, nasal cancer has not been observed in rats exposed to hydrochloric acid alone. In Dalbey's study of hamsters, hyperplastic and metaplastic areas were observed in the nasal epithelium of 5% of animals exposed to formaldehyde and none in controls, but no tumors were observed in those hamsters receiving formaldehyde. The Federal panel also considered the same issue and concluded that there was no evidence that "irritation," or induction of epithelial hyperplasia, is sufficient to account for the formaldehyde carcinogenicity (*70*). However, the panel did recognize that the induction of epithelial hyperplasia may contribute, to some extent, to cancer activity by enhancing stages of carcinogenesis such as tumor promotion or tumor growth.

XI. EPIDEMIOLOGY

Information on the acute and chronic health effects of formaldehyde in humans comes largely from (1) controlled human exposure studies, (2) case reports of individuals who were exposed to formaldehyde, and (3) cross-sectional studies in which measurement of exposure (formaldehyde) and effects (prevalence of symptoms, signs, and disease) were made at the same time among individuals repeatedly exposed to formaldehyde in residential or occupational settings. In addition, limited information on the carcinogenicity of formaldehyde is available from cohort and case-control studies in which the ascertainment of exposure and effects relate to two different points in time.

A. Controlled Human Exposure Studies

Several controlled experiments with increasing concentrations of airborne formaldehyde have been conducted on healthy volunteers to investigate its acute effects.

Andersen (*8*) studied the effects of formaldehyde on airway function, comfort perception, and learning capacity in 16 healthy young men exposed for 5 h to either 0.25, 0.42, 0.83, or 1.6 ppm formaldehyde. The exposures occurred in a climate chamber at 23°C and 50% relative air humidity. No significant changes in pulmonary functions (vital capacity $FEV_{1.0}$, $FEF_{25-75\%}$) or in performance on mathematical tests were reported between the control period and the period of exposure to formaldehyde. However, there was a significant reduction in mucociliary function at all concentrations except for 0.83 ppm. Subjective perception of discomfort, namely eye irritation and dryness in the nose and throat, was reported even at the lowest exposure, and the number of complaints increased with increasing formaldehyde levels. After exposure to 0.25, 0.42, 0.83, and 1.6 ppm formaldehyde, 3, 5, 15, and 15, respectively, of the 16 volunteers had complained of eye irritation and dryness of the nose and throat. The author concluded that the formaldehyde concentrations should be lower than 0.25 ppm in order for a 5-h exposure not to cause mucous membrane irritation and reduction in the natural clearance mechanisms of the mucous membranes.

In a second study, two separate experiments were conducted using a 30 m^3 climatic chamber (*245*). In the first experiment, 33 healthy students (24 men and 9 women) were exposed for 37 min to formaldehyde concentrations continuously rising to a maximum of 3.2 ppm. Every 5 min the subjects filled out questionnaires and their eye blinking rates were measured. In the second experiment, 48 healthy students (35 men and 13 women) were divided into four groups and subjected to five exposures of 1.5 min each and varying formaldehyde concentrations (0, 1, 2, 3, and 4 ppm). Between two exposures, the subject could recover for 8 min in the well-ventilated room. In both experiments, eye, nose, and throat irritation increased as a function of increasing formaldehyde concentration. The authors concluded that, on the average, significant changes in physiological parameters and comfort perception occurred at the following concentrations of formaldehyde: eye irritation, 1.2 ppm; nose irritation, 1.2 ppm; throat irritation, 2.1 ppm; annoyance (desire to leave the room), 1.2 ppm; eye blinking rate, 1.7 ppm. They also reported that at 2.1 ppm of formaldehyde exposure, 10% of the subjects experienced moderate eye irritation, 7% of the subjects had strong or very strong eye irritation, 33% of the subjects exhibited a doubling of eye blinking rate, and 20% expressed a desire to leave the room. In light of these observations, the authors suggested that a TLV of 2 ppm might be too high.

In a third study (*192*), a number of volunteers (5 or 10 at each exposure level) were exposed to 0, 0.1, 0.2, 0.5, 1.0, 3.0, or 5.0 ppm of formaldehyde for 1 h. Predominant complaints were eye, nose, and throat irritation, tear flow, nasal secretion, and awareness of objectionable odor. The total sum of complaints (frequency times intensity) was clearly dose dependent and at 0.2 ppm and above the responses differed significantly from control values.

These experimental studies demonstrate that upper respiratory tract irritation and eye irritation occur at formaldehyde concentrations of 0.2 ppm and above. The subjects of the experiments were healthy young adults, who may be less susceptible to the irritant effects of formaldehyde than people with allergy, children, and the elderly who are already suffering from respiratory tract illness. Also, the duration of exposure was short compared to consumer and industrial exposure.

On the basis of the studies by Andersen (*8*) and Weber-Tschopp *et al.* (*245*) and other available animal and human studies, the National Academy of Sciences concluded that there is no population threshold for the irritant effects of formaldehyde (*169*).

B. Case Reports

Numerous case reports of ill health associated with formaldehyde are available. Contact urticaria was described in a 28-year-old woman who worked as a carver and model setter in a factory in which leather dresses were manufactured (*106*). The leather contained small amounts of formaldehyde. She had urticaria almost daily (severely on the hands, with occasional edema of the lips) during the work week. During weekends and vacations, when she did not come into contact with leather, there was no evidence of urticaria.

A second case of contact urticaria was reported by Lindskov (*146*). A 26-year-old female who worked in a pathology laboratory for 8 years suffered daily outbreaks of urticaria of the face, neck, forearms, and dorsa of the hands. This occurred whenever she fixed tissue specimens. The rashes developed 15 min after she started working at the fume cupboard and disappeared a few hours after work was finished. The tissues were fixed in 10 and 20% solutions of buffered formaldehyde. The woman was transferred to other work in the laboratory and the urticaria disappeared. Similarly, Harris (*99*) described four persons who developed acute papulovesicular eczema following contact with urea–formaldehyde resins. The condition persisted until the workers were reassigned to areas without formaldehyde.

Sakula (*200*) reported a case of acute respiratory distress in a hospital laboratory technician following exposure to formalin. Severe bronchial asthma followed the slightest inhalation of formalin vapor, but the worker was free from attacks on weekends and holidays. A case of pneumonitis following heavy exposure to formaldehyde by inhalation has been reported (*189*). The case involved a 27-year-old neurology resident who spent 15 h exposed to high concentrations of formaldehyde vapor during preparation of brain specimens for student demonstrations. The following week, after only 2 h spent at the same activity, he developed acute respiratory distress including progressive dyspnea and chest tightness over a period of 15 h. Chest X rays showed increased interstitial markings with early edema. Decreased pulmonary function as measured by FVC, $FEV_{1.0}$, and MMEF was also noted on day 2 and day 24 after the onset of symptoms. This is said to be the first report describing a clinical picture of acute pneumonitis in man following formalin inhalation.

A number of employees of a dress shop reported burning, stinging eyes, nose and throat irritation, and headaches (*25*). Formaldehyde was found to off-gas from wrinkle-proof apparel and its concentrations in the shop ranged from 0.13 to 0.45 ppm. Similar symptoms were reported among workers involved in a paper conditioning process. The workers processed wood pulp paper which was previously treated with urea–formaldehyde or melamine–formaldehyde resin for shrinkage control. Air samples collected in the breathing zone of the workers revealed formaldehyde concentrations ranging from 0.9 to 1.6 ppm (*164*).

The United States Consumer Product Safety Commission has received over 3000 complaints involving formaldehyde vapor released from building materials: about 2000 involve urea–formaldehyde foam insulation and the remainder involve plywood, particle board, paneling, and other wood products. Predominant symptoms reported in the complaints were nausea, eye, nose, and throat irritation, headache, vomiting, and stomach cramps. Exposure data compiled by the CPSC on average formaldehyde levels in homes are as follows: homes without UFFI, 0.03 ppm; homes with UFFI, 0.12 ppm; mobile homes, 0.38 ppm; ambient air, 0.01 ppm.

C. Cross-Sectional Studies

Numerous cross-sectional studies of workers, volunteers, or residents exposed to formaldehyde reported health problems. Adverse health effects associated with formaldehyde exposure include eye, nose, and throat irritation, sneezing, shortness of breath, sleeplessness, tight chest, nausea, and excess phlegm (*77, 85, 129, 192, 203, 205*).

A recent study of Wisconsin mobile home residents reported that some of the above symptoms were significantly associated with the level of formaldehyde in the homes (*7*). Residents of 137 randomly selected mobile homes were enrolled for a 6-month prospective double-blind observation. Each month the residents filled out health questionnaires and after about 6 months the residents filled out a more detailed comprehensive health questionnaire and were asked to attend one of three clinics for a physical examination. Spirometry and single-breath diffusing capacity tests were also performed on all the participating residents over the age of 12. Formaldehyde levels in the homes were measured every month. Prevalence of burning eyes increased significantly with increasing mean formaldehyde levels in the homes. However, the presence of cough was not associated with the level of formaldehyde in the homes. The prevalence of clinical signs of irritation correlated with increasing mean formaldehyde levels in the homes: <0.4 ppm, 10%; >0.4 ppm, 24%; >0.8 ppm, 56%. The mean formaldehyde level in the homes of those who had clinical signs of irritation was 0.7 ± .3 ppm, while, for those without signs, the mean level was 0.4 ± 0.3 ppm. This difference was statistically significant. Results of spirometry were not associated with formaldehyde levels.

Similar effects were reported at even lower concentrations among German school children (*33*). The children were exposed to formaldehyde from urea–formaldehyde resin used for panels, acoustic ceilings, and school furniture. The mean formaldehyde concentrations ranged from 0.13 to 0.57 ppm. The study group (n = 1594) had a significant increase in upper respiratory irritation, eye irritation, and functional disturbances (headache, lack of concentration, dizziness, nausea) compared to a control group (n = 497). A substantial reduction of symptoms (71%) was reported 8 months after removal of the formaldehyde emission sources.

The irritant effect of formaldehyde on the upper respiratory tract and eyes was also reported in a recent study of New Zealand workers (*18*). The exposure group consisted of 110 workers employed in particle board manufacturing plants (n = 30), furniture manufacturing (n = 18), pathology laboratories (n = 28), chemical manufacture (n = 13), fiberglass products (n = 14), and other industry (n = 7). Formaldehyde levels, when measured in a few workplaces, ranged from 0.1 to 2.4 ppm; but total aldehyde levels for most workplaces were generally less than 1.0 ppm. A control group consisted of 56 government employees who were free of known formaldehyde exposure. Significant differences between the two groups in the prevalence of eye, nose, and throat irritation were reported. However, prevalence of lower respiratory tract symptoms with the exception of breathlessness, was not significantly different between the two groups.

An outbreak of hemolytic anemia among patients on hemodialysis was described in a recent report (*176*). The outbreak occurred shortly after a new system using filters impregnated with formaldehyde resins was installed. When the filters were removed, hematocrit values returned to previous levels. The severity and incidence of some responses were related to the concentration of exposure.

Other health effects attributed to formaldehyde from cross-sectional studies include respiratory problems, dermatitis, neurologic difficulties, and menstrual and reproductive disorders. Schoenberg and Mitchell (*205*) studied five groups of employees from a filter manufacturing plant to determine adverse effects of exposure to phenolic (phenol–formaldehyde) resin fumes. Groups of workers currently exposed to phenolic resins showed an excess of chronic cough and/or phlegm when compared to previously exposed workers or "never-on-line" workers who had never been production-line workers or supervisors. In addition, after adjustments were made for differences in total cigarette consumption, workers on the present production line for more than 5 years had a significantly lower $FEV_{1.0}/FVC$ and $MEF_{50\%}/FVC$ ratio ($p < 0.05$) than the never-on-line group. These results suggest that long-term exposure to phenol–formaldehyde resin fumes may lead to chronic airway obstruction. No systematic measurement of formaldehyde concentration was made during this study but, based on measurements by others, levels of formaldehyde were estimated to be in the range of 0.4 to 0.8 ppm. Exceptionally high levels (8.8–13.5 ppm) could occasionally occur when cross-current fans were turned off. In this plant, even never-on-line workers were occasionally exposed to resin fumes, which may explain the high prevalence of acute symptoms such as eye irritation (80%), nose irritation (53%), and lower respiratory tract symptoms (47%) among these workers. As noted by the authors, the limitations of this study include small numbers of exposed subjects, probable formaldehyde exposure among the never-on-line workers, and the potential for selective bias commonly associated with cross-sectional studies. In addition, the possible role of the parent resins, phenol, and other exposure from the industrial process prevent a clear determination that long-term exposure to formaldehyde may lead to chronic airway obstruction.

In a study of rubber workers exposed to hexamethylenetetramine–resorcinol (HR) resins, Gamble *et al.* (*84*) found more self-reported symptoms (itch, rash, cough, chest tightness, burning eyes, running nose, and persistent cough and phlegm) among HR-exposed workers than among nonexposed workers. Contrary to the previous findings of Schoenberg and Mitchell (*205*), there were no differences in lung function between HR-exposed workers and nonexposed workers. There were, however, significant differences in lung function measurements before and after the regular work shift for HR-exposed workers, but not among the nonexposed workers. The resin investigated in this study was composed of resorcinol as the phenol donor and hexamethylenetetramine (HMT) as both a formaldehyde donor and a catalyst. There was no association between decreases in lung function and ambient levels of resorcinol, formaldehyde, hydrogen cyanide, or ammonia. Mean concentrations of formaldehyde were 0.05, 0.01, and 0.04 ppm for HR-exposed, non-HR-exposed, and control groups, respectively. The decrease in pulmonary function was related to the quantity of respirable particulates obtained from personal samples. Chemical analysis of particulates, however, was not performed.

In a study of 73 workers exposed to phenolic (phenol–formaldehyde) resin dust in the textile industry, Sparks and Peters (*219a*) reported a statistically significant acute drop in $FEV_{1.0}$ and FVC over the shift in garment-line workers exposed to the phenolic resin dust. Workers exposed only to processed cotton dust did not show a significant drop in $FEV_{1.0}$ and FVC over the work shift. The limitations of this study include no measurement of formaldehyde levels, small number of study subjects, a high rate of absence and refusal, mixed-dust exposure, and use of respirators. In spite of these limitations, the study suggests the possible role of formaldehyde in inducing chronic obstructive effects on lung function.

A significant reduction in $FEV_{1.0}$ and other pulmonary functions after a day of work was reported among 47 workers exposed to formaldehyde (*4a*). Exposure to formaldehyde (mean, 0.36 ppm; range, 0.04–1.25 ppm) occurred in the area where sawdust and wood chips were cemented together under high pressure in the process of manufacturing chipboard. Another 20 workers from the same plant (at the carpentry works), but not exposed to formaldehyde or other agents known to irritate the lung, were also examined. In addition to the usual symptoms such as irritation of eyes, nose, and throat, workers exposed to formaldehyde displayed a significant reduction in lung function irrespective of their smoking status: $FEV_{1.0}$ decreased by an average of 0.17 liter, $FEV_{\%}$ decreased by 2.4%, MMF decreased by 0.39 liter/sec, and $CV_{\%}$ increased by 3.4%. These findings are consistent with signs of airway obstruction, which apparently subsides over the weekend of nonexposure, as evidenced by the normal lung function on Monday morning before work.

A study of 199 workers involved in the manufacture and processing of formaldehyde did not show any significant difference in lung function, nor did the workers demonstrate abnormal lung X-ray or blood biochemical parameters as compared to a control group consisting of 91 steel construction workers (*92*). The majority of formaldehyde workers in this study was exposed to less than 0.2 ppm formaldehyde. Under this exposure condition, the study could not demonstrate that the workers suffered from chronic impairment of health.

Eight cases of occupational asthma (three smokers and five nonsmokers) were reported among 28 members of the nursing staff of a hemodialysis unit where formalin was used to sterilize the artificial kidney machine (*108*). Recurrent episodes of productive cough accompanied by wheeze were a prominent feature and, for five persons, attacks had extended over the previous 3 years. Inhalation provocation tests were performed on the five subjects with histories of recurrent attacks of wheezing. In two of these subjects, the test resulted in asthmatic attacks like those experienced at work. Peak expiratory flow rates fell approximately 50% and wheezing began 2 and 3 h after exposure to formalin and lasted for 10 h to 10 days. Three of the five subjects had no respiratory reaction to inhalation of formaldehyde similar to that experienced in the dialysis unit. Two of the five had no symptoms, and one developed conjunctivitis. This latter patient developed redness, weeping, and sensations of grittiness of the eyes when heavily exposed to formalin. In the absence of symptoms and exposure, there was no apparent reduction in lung function. The authors suggested that although formalin may not have been the etiologic agent in all cases, it may have increased the susceptibility to other agents, which could, perhaps, explain the high incidence of bronchitislike symptoms. In the absence of a comparison group, an alternative explanation of the asthma being attributable to chance alone still exists. However, the explanation is unlikely because of the high proportion of the staff that developed the symptoms and because of the positive responses observed after the inhalation provocation test.

Formaldehyde-related asthma and dermatitis were also reported by Kerfoot and Mooney (*129*). A survey of six Detroit area funeral homes conducted by the authors showed that embalmers were generally exposed to formaldehyde at mean levels ranging from 0.25 to 1.39 ppm, with a total range of 0.09–5.26 ppm. They experienced acute toxic effects including eye and nose burning, sneezing, coughing, and headaches. Asthma or sinus problems were reported by three out of seven morticians. In addition, two workers experienced dermatitis, with one case being so severe that the worker discontinued working for a period of time until he recovered. Embalming agents contain formaldehyde as well as a variety of other chemicals such as tissue moisturizers, smooth muscle relaxants, bleaches, an auxiliary antiseptic agent (phenol), dyes, buffers, wetting agents, water conditioners and/or anticoagulants, perfumes and odor suppressors, and vehicles (methanol, ethanol, and glycerin). In light of the possible mixed exposure to a variety of the above chemicals during embalming, and the lack of an appropriate control group in the study, the relationship of formaldehyde exposure among embalmers to development of asthma and dermatitis remains inconclusive.

In a mail survey of 20 funeral homes in Los Angeles, 57 of 80 embalmers responded (*187*). Nine (16%) reported symptoms compatible with acute bronchitis and 17 (30%) were considered to have chronic bronchitis. The 31 asymptomatics, however, had worked longer than the bronchitics (18 vs 11 years). In the absence of a control group and in light of the possible mixed exposure to other chemicals, these findings are, at best, only suggestive of the role of formaldehyde in development of bronchitis.

Engle and Calnan (*65*) reported an outbreak of dermatitis in a car factory. A total of 50 cases of dermatitis was observed in 3 years (1962–1965) among 150 employees who handled rubber weather strips coated with phenol–formaldehyde resins. The workers who developed dermatitis had been exposed to the adhesives containing phenol–formaldehyde resins for from 1 day to 2 years before the onset of the eruption, with an average period of contact of 17 weeks. The average duration of the eruption was 12 weeks; however, in three cases it persisted for up to 2.5 years. The eruption was generally an erythematous vesicular rash of the fingers and hands. Three materials were handled by these employees: (1) the rubber weather strips, used for some years, (2) adhesives A and B introduced 4 years before in 1962 and supplied by the same manufacturers, and (3) toluene, which was the solvent used to activate the adhesive. The rubber weather strips alone were ruled out as a cause because they came from various suppliers and had not changed in composition for a long time: toluene would not be expected to cause sensitization. Among the 29 patch-tested dermatitis patients, 4 (14%) gave a weak reaction to phenol alone, while 65% had a positive reaction to the adhesive resins. It is, therefore, probable that formaldehyde in the resins was a causal agent.

Outbreaks of dermatitis in several industries using formaldehyde resins were reported by Schwartz *et al.* (*207*). In a factory in which plywood was laminated, 600 cases of dermatitis were reported among about 800 workers during the first 6 months of operation. In a second reported outbreak, over 40 workers out of a total of 100 developed dermatitis in a factory in which tool handles were made from laminated glass fabric and phenol–formaldehyde resins. Although no unexposed group was available for comparison, the high proportion of formaldehyde-exposed workers developing dermatitis is quite impressive.

In a hemodialysis unit in which formalin was used as a sterilant, 6 of 13 staff members developed dermatitis within 3 weeks (*218*). Four of the six gave positive patch tests to 3% formalin. It was not clear why only the hemodialysis unit was affected since other units also used formalin. The author speculated that it might be due to the use of a detergent that lowered the resistance of the skin to formaldehyde vapors and to the high temperature and concentration of formalin in the preparation room.

Shumilina (*214*) reported a high incidence of menstrual and reproductive function disorders among 446 women workers (130 finishers and 316 inspectors) exposed to urea–formaldehyde resins. Formaldehyde concentrations of 1.2–3.6 ppm were often found in the finishers' work area of the fabric trim shop, while levels from 0.04 to 0.06 ppm occurred in the inspectors' work area. A group of 200 saleswomen not exposed to formaldehyde was used for comparison. The reproductive disorders reported to be more common among those exposed, primarily in finishers, included menstrual disorders, increased complications during pregnancy, and a higher percentage of neonates with low birth weights. The role of formaldehyde in the development of these disorders is uncertain, however, because of the lack of information on the work environment and the socioeconomic status of the study and control groups. In addition, many of these disorders are known to be associated with physical and mental stress, personal habits (alcohol, cigarette, and caffeine consumption), nutritional status, and other factors related to the socioeconomic status of women. More recently, Olsen and Døssing have reported that female workers in mobile home day care centers experienced significant increases in irritation of mucous membranes, tiredness, headaches, and menstrual irregularities when compared to control workers (*175a*). These workers were exposed to a mean formaldehyde concentration of 0.43 ppm whereas control workers were exposed to 0.06 ppm. The findings reported by Shumilina and by Olsen and Døssing are intriguing and indicate a need for further studies in this area.

Neshkov and Nosko (*173*) reported a high incidence of sexual dysfunction among male workers employed in a plant producing glass fiber-reinforced plastic. These workers were exposed to vapors of phenol, formaldehyde, aniline, epichlorohydrin, styrene, and a combination of glass fiber and glass-reinforced plastic dust. The levels of each of these chemicals were 1.5 times the respective maximum permissible level (0.4 ppm) in 63% of the samples. Among the 143 workers examined, 58 (40.5%) had psychoneurologic and sexual complaints. Sexual complaints included a diminution of libido, premature ejaculation, a weakening erection, and decrease in the satisfaction derived from an orgasm. Analysis of the sexual complaints revealed a direct relationship to the duration of employment at the plant. Testicular dysfunction among the workers was also reported, including decreased volume and increased viscosity of ejaculate and decreased number of spermatozoids. The authors concluded that these sexual dysfunctions were the results of complex toxic effects of chemicals on the cells of the cortex and those of the subcortical brain stem structures, which participate in the regulation of sexual function. It is impossible to determine how much of the sexual dysfunction might be attributable to formaldehyde since appropriate control groups were not included and these workers were exposed to a variety of toxic chemicals in addition to formaldehyde. Of particular interest are reports of epichlorohydrin-induced sterility in animals (*46, 124*).

D. Cohort and Case-Control Studies

Epidemiologic studies available for review in these categories involved two classes of workers: (1) those from occupations or industries in which formaldehyde exposure may have occurred, and (2) those from occupations or industries in which formaldehyde exposure has definitely occurred.

Studies involving the first class of workers were not designed to evaluate the role of formaldehyde in the development of disease or cancer. Although the studies did not specifically specify exposure to formaldehyde, they were included because of the likelihood of their exposure to formaldehyde.

Moss and Lee (*165*) have reported elevated risks of oral and pharyngeal cancers among male textile workers. They reported 77% excess deaths due to these cancers compared with the general male population of Wales and England. These textile workers may have been exposed to formaldehyde, since formaldehyde has been widely used in the textile industry for producing creaseproof, crushproof, and shrinkproof fabrics. No environmental measurements of formaldehyde, however, were made in this study. A recent NIOSH survey showed concentrations of formaldehyde in textile plants in the United States ranging from 0.1 to 1.4 ppm. Bross *et al.* (*30*) reported a significantly increased risk of nasal cancer among textile workers and shoemakers. Textile workers also had a significantly elevated risk of cancer of the pancreas and stomach. No information on formaldehyde concentrations was reported.

Decoufle (*54*) has reported significantly increased risks of cancer of the buccal cavity, pharynx, and larynx among male leather workers. Bladder cancer and malignant lymphomas were also associated with increased risks among male and female employees in the leather industry. The cancer risk for these employees was calculated relative to the risk for those who were in clerical positions. A variety of chemicals including formaldehyde, azo dyes, chromium compounds, and tanning extracts has been used in the production of leather goods. Some of these chemicals are carcinogenic in animals. Industrial hygiene surveys of a calfskin tannery in the United States showed concentrations of formaldehyde in the finishing department ranging from 1 to 8.6 ppm.

In contrast to the above studies of industrial workers, many studies of medical personnel, i.e., physicians, pathologists, and laboratory technicians, did not indicate cancer hazards. Medical personnel, particularly pathologists and certain laboratory technicians, are very likely to be exposed to formaldehyde. Doll and Peto (*59*) studied mortality rates of a total of 20,540 British male doctors by their specialties. The follow-up was from 1952–1971, and the number of observed deaths was compared to the expected deaths calculated from the general male population. No excess deaths from cancers of either lung, mouth, or esophagus, or from other cancers were reported among the 853 physicians classified as laboratory scientists (pathologists and biochemists).

Harrington and Shannon (*98*) studied the mortality pattern of pathologists and medical laboratory technicians in the United Kingdom. Mortality patterns of a total of 2079 pathologists alive and active at some time between 1955 and 1973, and a total of 12,944 medical technicians who registered between 1963 and

1973, were followed up to the end of 1973 and compared with those of the population of England and Wales or Scotland. During the study period, 156 pathologists and 154 medical technicians died. No excess deaths from cancer of the lung, bronchus, trachea, digesive tract and peritoneum, or bladder were reported in either group. However, in male pathologists in England and Wales, a statistically significant increase in lymphatic and hematopoietic neoplasms was observed (8 observed vs 3.3 expected, $p < 0.01$). The mortality data were not analyzed for nasal or pharyngeal cancers.

Jensen and Andersen (*121*) reported a case-control study of lung cancer risk among Danish physicians. Information on the medical specialty of 84 physicians who died from lung cancer was compared with the information for 252 controls. The controls were also physicians and were matched with the cases by age, sex, and survival, at least until the time of lung cancer development. Physicians who specialized in pathology, including forensic medicine and anatomy, did not show an unusual risk of lung cancer death. In fact, none of the 84 lung cancer victims were pathologists. Furthermore, previous employment at some time during their professional careers in pathology, forensic medicine, or anatomy was not associated with the increased lung cancer risk. Jensen (*120*) reported earlier that during the period 1943–1976 three cases of cancer of the nasal cavities, sinuses, and nasopharynx were observed in Danish doctors. However, none of these three physicians had ever worked in a pathology department or as an anatomist.

In all these studies of industrial workers and medical personnel, actual exposure to formaldehyde is not known. The lack of information concerning the number of persons actually exposed to formaldehyde and the level of their exposure, in addition to confounding exposures to other chemicals, makes interpretation of these reports regarding formaldehyde difficult.

The second category of studies includes investigations designed specifically to evaluate health hazards of formaldehyde among workers who were employed in areas where formaldehyde was produced or used. Since 1980, several mortality studies of workers who had been potentially exposed to formaldehyde have been reported. Wong (*248*) studied a cohort of 2026 white males who were ever employed through 1977 at a chemical plant in which formaldehyde and other chemicals were produced. The plant was built in the early 1940s and, in addition to formaldehyde, handled a variety of substances, such as oxygenated hydrocarbons, benzene, asbestos, and inorganic and organic pigments. The cohort was followed through December 31, 1977. A total of 146 deaths was observed. Vital status was not ascertained for 51 workers. Death certificates were obtained for all but 10 of the individuals known to have died. The number of expected deaths was calculated based on mortality rates for white males in the United States. Mortality from cancer at all sites for the entire cohort was not different from that expected (37 vs 36.5). Excess SMR values were observed for cancer of the prostate (4 vs 1.31) and brain (3 vs 1.61), and for Hodgkins disease (2 vs 0.83).

But none of the increased SMR values was statistically significant. Limiting the analysis to deaths that occurred more than 30 years after first employment in the plant, the author found a statistically significant excess of deaths from prostatic cancer (4 vs 0.93). There were no deaths observed from cancers of the nose or nasal sinuses. Analysis of data by the proportionate mortality ratio (PMR) revealed significantly elevated PMR values for all cancer (PMR = 148), cancer of the bone (PMR = 625), and cancer of the prostate (PMR = 367). The role of formaldehyde in the development of cancer is difficult to determine from this study for a number of reasons. First, the study includes all white males who were ever employed at the plant between the early 1940s and December 1977. But no information is given as to what proportion of these workers was actually exposed to formaldehyde and for how long. Second, only a small number of individuals had achieved 20+ years of latency, limiting the chance of identifying a carcinogenic risk from exposure to formaldehyde. Third, the size of the cohort is too small to detect any risk of nasal cancer even if excess nasal cancer was actually induced by formaldehyde: there was only an 8% probability of detecting a threefold increase in risk of death from nasal cancer.

Marsh (*153*) conducted a proportional mortality analysis on 136 deaths occurring between 1950 and 1976 among male workers who had worked for at least 1 month in areas of the plant where exposure to formaldehyde as well as to other chemicals would have occurred. Only 36 decedents had spent the largest portion of their employment in plant areas where significant formaldehyde exposure could have occurred routinely. The number of observed deaths was compared to expected numbers calculated by applying the cause-specific proportional mortality of United States white and nonwhite males to the total number of white and nonwhite deaths in the study group after adjusting for age and time period. In general, the PMRs for all cancer and specific cancer sites were not significantly different than expected, with the exception of cancers of the digestive organs and peritoneum. When analyzed by age at death, the youngest of the three age groups (45, 45–64, 65+) of white male formaldehyde-exposed workers indicated excess mortality from cancer of the digestive tract (PMR = 413, 2 observed deaths). Among those white males exposed for a total of less than 5 years and with more than 20 years from onset of exposure, the PMR for cancer of the digestive tract was 320 (5 observed deaths). No sinonasal cancer deaths were observed in the study. The mortality data were not analyzed separately for pharyngeal cancer. This study also is inadequate to assess the carcinogenicity of formaldehyde in humans because (1) very limited information on formaldehyde exposure is available, (2) a very small number of decedents ($n = 36$) could have had actual exposure to formaldehyde for a significant portion of their employment, and (3) the small number of deaths gives the study limited power to detect increases in mortality from nasal cancer: there was only a 7% probability of detecting a threefold increase in risk of death from nasal cancer.

A study of the same plant population as above, however, followed further through 1980 by another group of investigators showed different results. In a recent meeting, Liebling *et al.* (*145a*) reported a PMR analysis of those who died between January 1, 1976 and December 31, 1980. Among 211 decedents identified during this 5-year period, 24 workers appeared on seniority lists from work areas with known formaldehyde exposure. An analysis based on the 24 deaths indicated statistically elevated PMRs for buccal and pharyngeal cancer (2 observed, PMR = 870). The worker who died of pharyngeal cancer had a squamous cell cancer, which is the same histologic type as developed in experimental animals exposed to formaldehyde.

A team of NIOSH investigators has reported a case of squamous cell carcinoma of the nasal cavity in a 57-year-old worker who had 25 years of occupational exposure to low concentrations of formaldehyde in the textile finishing industry (*95a*). A recent survey at a fabric finishing plant in the United States indicated that formaldehyde concentrations in air ranged from 0.2 to 1.2 ppm; exposures may have been higher in the past when more highly concentrated solutions were used (*64a*). Workers involved in a textile finishing operation also are likely to be exposed to sodium hypochlorite, as well as to dyes, dye carriers, and antifoaming agents. Cancers of the nasal cavity and sinuses are very rare tumors. The annual incidence among United States males is approximately 8 per million for a lifetime risk among United States males of about 6 per 10,000—about the same as the lifetime risk for breast cancer in males. As much as the reports of nasal and pharyngeal cancer cases in workers exposed to formaldehyde may help to generate an etiologic hypothesis, they would hardly be expected to provide evidence of causation or lack of causation.

Walrath and Fraumeni (*241*) studied the proportion of cancer deaths in a group of 1106 deceased embalmers who had been licensed to practice embalming in New York State between 1902 and 1979. Formaldehyde has been the main preservative in commercial embalming fluids and its use in embalming fluids is required by various state laws in the United States. The number of observed deaths due to specific causes was compared to the expected numbers calculated by the same method described in the Marsh study. The PMR value for all cancers was slightly elevated. However, the study shows an unusually high PMR for death from skin cancer among white male embalmers. The excess was greater among those licensed for more than 35 years than among those licensed for less than 35 years (PMRs of 196 vs 354), among those licensed after age 30 than those licensed before age 30 (PMRs of 151 vs 424), and among those licensed for embalming only than those licensed for both embalming and funeral directing (PMRs of 337 vs 178). The proportionate mortality for kidney and brain cancers also was elevated among white males licensed only for embalming. No excess mortality from cancers of the respiratory tract was reported. Despite the limitations of the PMR study, a high magnitude of excess PMRs as well as an upward trend by years since first licensed and the type of license suggest a role of formaldehyde in the development of skin cancer among embalmers.

A case-control study of du Pont chemical plant employees who had died from cancer was recently reported (*69*). A total of 481 cancer deaths from 1957 to 1979 among male employees at eight formaldehyde-manufacturing and -using plants was compared to an equal number of du Pont employees who were known to have not died from cancer (controls). Each cancer case was matched to a control for age (± 3 years), plant location, sex, pay class (wage or salary), and adjusted service date (± 3 years). Information on work histories for both cases and controls was obtained from personnel records, medical records, or co-worker interviews. The potential for exposure to formaldehyde for each job was estimated on the basis of several factors, including job descriptions, air-monitoring data, and statements by employees concerning odor or sensory irritation. The data were analyzed by tumor site, latent period, duration of exposure, exposure level and frequency, cumulative exposure index, age and year of death, and age and year of first exposure. Analyses of lung cancer deaths were adjusted for subjects' cigarette smoking habits. The study did not show a significantly elevated relative risk of cancer in any of the above analyses. No nasal cancer deaths were observed. The authors concluded that cancer mortality rates for formaldehyde-exposed du Pont workers were no higher than the rates among nonexposed co-workers. They further state that airborne formaldehyde levels of 1 ppm TWA and a 2 ppm ceiling provide adequate worker protection. This study should be considered preliminary, however, until certain limitations are accounted for. First, a major limitation of the study is the possibility of observation bias: all controls were identified from lists of active employees, whereas all cases were dead when identified. Second, the cases and controls may have been overmatched on factors related to exposure of interest, limiting the study's ability to detect differences in the degree of exposure between cases and controls. Third, for most of the site-specific cancers studied, the number of workers who died from these cancers was too small to reliably detect moderately elevated relative risks of cancer resulting from formaldehyde exposure.

In a recent meeting, Levine (*143*) reported a mortality study of 1477 male undertakers who were first licensed in Ontario, Canada between 1928 and 1957. The cohort was followed through December 31, 1977. A total of 337 undertakers was known to have died. Vital status of 209 undertakers was not ascertained. All undertakers were potentially subjected to formaldehyde exposure during embalming. The number of expected deaths was calculated based on mortality rates for United States white males, because death rates for Canadian males were not yet available in suitable computer format. Deaths from all causes (337 observed vs 370.1 expected) and all cancers (60 observed vs 67.7 expected) were not significantly higher than expected. No deaths due to nasal cancer or skin cancer were observed. Mortality from cancer of the prostate (2 observed vs 3.1 expected), kidney (1 observed vs 1.8 expected), and lung (19 observed and 21.3 expected) was less than expected. Cirrhosis of the liver was the only cause of death reported to be significantly in excess (18 observed vs 10.5 expected). The author speculated that the excess for cirrhosis of the liver might be attributable to increased alcoholism among the undertakers. However, other deaths related to alcoholism, such as deaths from suicide or accident, were less than expected. Whether the cirrhosis may have been due to formaldehyde or its metabolite in the liver cannot be determined at this time. No analyses of the mortality data by magnitude of formaldehyde exposure were presented. It should be noted that the undertakers also included funeral directors who had no or minimum contact with bodies or the chemicals used to treat them. The embalmers' exposure to formaldehyde was reported to be intermittent (a few hours/week) and low (less than 1 ppm) when it occurred. The embalmers in small towns may experience no exposure at all during some years. Until the mortality data are fully analyzed and published, the findings should be considered preliminary.

XII. SUMMARY AND CONCLUSIONS

As this and other reviews indicate, formaldehyde is a ubiquitous chemical. Exposure can occur in homes, workplaces, and the general environment. Small amounts of formaldehyde can cause adverse health effects and, since many of those exposed to it may not perceive or recognize its odor, the sense of smell cannot be relied upon to give warning against its possible adverse health effects.

At present, the ambient air concentrations of formaldehyde appear to be best characterized in mobile homes, in homes containing urea–formaldehyde foam insulation, and in some workplaces. Data on other sources of exposure are more limited. Formaldehyde that is present in homes probably poses the greatest potential health hazard, since people of all ages and states of health spend most of each day in their residences. Concentrations of formaldehyde in indoor air almost always exceed those in outdoor air. Products most likely to emit formaldehyde into the indoor air appear to be urea–formaldehyde resin-bonded wood products, such as particle board and plywood, and, until recently, urea–formaldehyde foam insulation. The relative contributions of the various unvented combustion sources in the home require additional characterization. More data are needed to define all of the factors involved in formaldehyde release from resins.

Formaldehyde is a very reactive chemical and readily combines with DNA, RNA, protein, amino acids, and a variety of other organic chemicals in the body. Conjugation of formaldehyde with low-molecular-weight biochemicals can facilitate intracellular reactions with DNA. Some animal carcinogens may act in a similar manner following metabolism to formaldehyde. Because endogenously formed formaldehyde is apparently metabolized very rapidly, it would not be expected to react with cellular macromolecules in the same way or to the same degree as exogenous formaldehyde. Nor would it be expected to pose the same health hazards.

The metabolic reactions of formaldehyde in humans and animals are similar. It has been found that body tissues can rapidly metabolize exogenous formaldehyde even at high concentrations, although some of this formaldehyde can still react with tissues and cellular macromolecules before being metabolized.

Formaldehyde is an irritant via all routes of exposure and can cause local damage to the eyes, respiratory tract, and skin when inhaled. The effects of formaldehyde may not be limited only to these tissues, since it forms conjugates with biological chemicals that may affect tissues that are remote from the respiratory tract. Thus, in some studies, there is evidence showing that formaldehyde causes adverse effects in tissues and organ systems that are not directly exposed, including the central nervous and hematopoietic systems, as well as the kidneys, adrenals, and liver. Effects in liver appear to be generally dose related, although, at present, the mechanisms by which these effects occur are unknown.

In the case of liver exposure, formaldehyde also may enhance the toxicity of chemicals and drugs that require glutathione for hepatic detoxification. Drugs requiring glutathione include aspirin, acetaminophen, and corticosteroids, all of which could be used to treat symptomatic effects resulting from exposure to formaldehyde, such as nausea and headaches and dermal irritation. Additional work is needed in this area.

Some individuals have become sensitized to formaldehyde following dermal contact and, perhaps, following inhalation exposure. Dermal contact with formaldehyde elicits both immediate and delayed reactions that are immunological in nature. Repeated exposure of susceptible individuals to formaldehyde via inhalation causes asthmatic reactions, which may be either immediate or delayed. The delayed reactions appear to be immunological in nature. Since asthmatic reactions involve the lower respiratory tract, elicitation of these reactions may depend upon the presence of airborne particulates to carry formaldehyde into the low respiratory tract.

The currently available data do not show that the embryo is unusually sensitive to formaldehyde nor is there any information to show that formaldehyde is teratogenic in rodents when administered orally or applied dermally in nontoxic amounts to the dams. Also, the *in vitro* data do not provide any evidence to support the conclusion that formaldehyde causes terata at exposure concentrations that are not toxic to the adult.

Inhalation of formaldehyde has caused fetotoxic effects but not teratogenic effects. Further studies of formaldehyde exposure by inhalation are needed to elucidate the meaning of these changes. Limited evidence suggests that formaldehyde may affect the menstrual cycle and perhaps reproduction in women repeatedly exposed. Additional work is needed to validate these findings.

Formaldehyde causes mutation and chromosomal aberrations in a wide variety of bacteria, yeasts, fungi, and insects in several test systems, as well as in some human cell test systems with and without metabolic activation. These effects are enhanced in excision repair-deficient test systems. In some testing systems, formaldehyde interacts with other mutagens resulting in a greater effect than either would cause alone. Formaldehyde has been shown to cause cell transformation in BALB/c 3T3 cells and to act as both an initiator and a promoter in C3H/10T1/2 cells. Chromosomal breaks and mutations have not been found in whole animal studies. A likely explanation for this latter finding may be that an insufficient dose reaches the target tissues. At present, there are very limited data indicating possible adverse effects on chromosomes in humans from formaldehyde exposure. Additional studies are needed to characterize whether there are any such effects directly attributable to formaldehyde.

Most of the carcinogenic studies on formaldehyde in animals done in the past have had certain limitations that made unclear the meaningful interpretation of the data. However, the results of recent long-term experiments in rats and mice conducted by Battelle for CIIT and studies by NYU both provide acceptable evidence that exposure to formaldehyde by inhalation causes squamous cell carcinomas in the nasal tissues of rats and mice. In addition, dose-related metaplastic and dysplastic changes were noted in the experimental animals, as well as adenomas of the nose at exposures as low as 2.0 ppm (the lowest dose tested). Formaldehyde may also cause cancer at other sites of exposure.

Several studies are now under way that may help to define the body defense mechanisms against the effects of formaldehyde, such as decreases in rate of respiration, tidal volume, or nasal mucous flow. The current data are not sufficient for a clear understanding of how effective such mechanisms actually are.

Under controlled exposure conditions, formaldehyde irritates the eyes, nose, and throat in healthy humans at concentrations as low as 0.2 ppm. The proportion of exposed individuals who experience any irritation and the degree of the irritation experienced increase as the concentration and duration of exposure increase. Effects would be expected to be more severe and to occur at lower concentrations in subpopulations that include the elderly or the infirm under conditions of chronic exposure.

Exposure to formaldehyde in homes and in workplaces may result in signs and symptoms attributed to the exposure, such as headache, dermatitis, chronic airway obstruction, and menstrual, reproductive, and sexual dysfunction, in addition to irritation of the eyes, skin, and mucous membranes of the nose and throat. The results of investigations that show these health effects are usually those given in case reports or cross-sectional studies. Many of these studies lacked appropriate controls and/or environmental exposure measurements, making it difficult to clearly establish formaldehyde as the causal agent. However, there has been some validation of the many independent reports of respiratory system disorders and of dermatitis in persons who are exposed to formaldehyde in a variety of environmental situations. Certainly not all of the reports have been or can be validated; however, the findings from many of them strongly indicate that formaldehyde is the major contributor to the observed adverse health effects. The reports of reproductive disorders among women who are exposed to formaldehyde are provocative. Although two independent epidemiological studies have shown that formaldehyde affects human menstrual cycles, there is still a question of uncertainty about these data that precludes making a firm conclusion. However, the implications of these studies are serious and far-reaching, owing to the ubiquitousness of the potential for exposure. The need for further research on the reproductive effects of formaldehyde in humans is both urgent and crucial.

Several epidemiological studies have been designed to evaluate the relationship between formaldehyde exposure and cancer in humans. These studies revealed significant increases in cancer of the prostate, digestive system, and upper respiratory tract associated with exposure to formaldehyde. All of these studies have limitations in design, methodology, sample size, information on exposure, patient follow-up, selection bias, or overmatching and exposure–effect associations. They do not provide definitive evidence upon which to evaluate the carcinogenicity of formaldehyde in humans. These limitations should be corrected in the design of future epidemiological studies of formaldehyde. In the interim, formaldehyde should be regarded as posing a carcinogenic risk to humans.

Concern over the known and potential health effects of formaldehyde has led to certain regulatory actions against products containing formaldehyde (UFFI and mobile homes) by various states, a city, and a federal agency (the Consumer Product Safety Commission). Standards to limit residential exposure to formaldehyde have been issued by various European countries. More recently, ASHRAE has recommended that formaldehyde levels in buildings not exceed 0.01 ppm.

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ITEM 5

Correspondence Between The Senate Special Committee On Aging And The Department Of Health And Human Services

11/25/85	Letter to Frank Young, M.D., Ph.D., Commissioner, Food and Drug Administration (FDA), from Senator John Heinz, Chairman, Special Committee on Aging, U.S. Senate. RE: committee staff access to FDA records and personnel concerning the committee's inquiry into regulation of the manufacture and use of hemodialysis devices.
2/21/86	Letter to Henry R. Desmarais, M.D., Acting Administrator, Health Care Financing Administration (HCFA), from Senator John Heinz, Chairman, Special Committee on Aging, U.S. Senate. RE: invitation for testimony at a hearing on March 6, 1986 concerning HCFA's policy regarding the reprocessing and reuse of disposable hemodialysis devices in the End Stage Renal Disease (ESRD) program.
2/21/86	Letter to Frank Young, M.D., Ph.D., Commissioner, FDA, from Senator John Heinz, Chairman, Special Committee on Aging. RE: Invitation for testimony at a hearing on March 6, 1986 concerning the FDA's policy in ensuring safety and efficacy in the reprocessing and reuse of hemodialysis devices.
2/28/86	Letter to Senator John Heinz, Chairman, Special Committee on Aging, from Lawrence J. DeNardis, Acting Assistant Secretary for Legislation, Department of Health and Human Services (DHHS). RE: acceptance of invitation for testimony at the committee's hearing scheduled for March 6, 1986.
6/13/86	Letter to Senator Heinz, Chairman, Special Committee on Aging, from Bartlett S. Fleming, Associate Administrator for Management and Support Services, Health Care Financing Administration, Department of Health and Human Services. RE: Investigation of complaints by witnesses appearing before the March 6, 1986 hearing on reuse, and acknowledgement of HCFA policy on reuse and on facilities which force their patients to reuse at the risk of being denied treatment.

JOHN HEINZ, PENNSYLVANIA, CHAIRMAN

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LARRY PRESSLER, SOUTH DAKOTA
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STEPHEN R. McCONNELL, STAFF DIRECTOR
DIANE LIFSEY, MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510

November 25, 1985

The Honorable Frank Young, M.D., Ph.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

As Chairman of the Special Committee on Aging, I am writing to request your assistance in the Committee's ongoing inquiry into utilization of the services and procedures in the Medicare and Medicaid programs.

Specifically, I am requesting that the Food and Drug Administration (FDA) provide to the Committee staff full access to all correspondence, studies, reports, memoranda, establishment inspection reports and attachments, computer and word processor-stored data and information, and any other records and documentation pertaining to the regulation of the manufacture and use of medical devices associated with hemodialysis.

In addition, I would very much appreciate your providing to the Committee by close of business on December 10, 1985 copies of any and all memoranda, correspondence, reports, meeting minutes and other records generated by the FDA and pertaining to the following: (1) the development and establishment by the FDA of standards for performance and disclosure in the reuse of such hemodialysis devices as dialyzers, blood tubing and transducer filters that are labeled for single use only; and (2) FDA findings on the safety and effectiveness of the reuse of such hemodalysis devices as dialyzers, blood tubing and transducer filters that are labeled for single use only.

I understand that the FDA established a "Reuse Committee" more than a year ago to address issues concerning reuse, and that minutes have been kept on committee meetings. Please provide the Committee with copies of these minutes by close of business on December 10, 1985.

As some of these documents and records may contain information of a sensitive nature, you have my personal assurance that these materials will receive appropriate treatment.

Should you have any questions regarding this request, please have your staff contact Jim Michie of the Committee Staff at 224-5364.

Thank you for your assistance and cooperation in this important matter.

Sincerely,

John Heinz

JOHN HEINZ
Chairman

JOHN HEINZ, PENNSYLVANIA, CHAIRMAN
WILLIAM S. COHEN, MAINE
LARRY PRESSLER, SOUTH DAKOTA
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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510

February 21, 1986

Honorable Henry R. Desmarais, M.D.
Acting Administrator
Health Care Financing Administration
Department of Health and Human Services
314G Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Desmarais:

As Chairman of the Special Committee on Aging, I am writing to request that you appear before the Committee on the morning of March 6, 1986 to provide testimony on the Health Care Financing Administration's (HCFA) policy regarding the reprocessing and reuse of disposable hemodialysis devices in the End Stage Renal Disease (ESRD) program.

A four-month Committee staff investigation has revealed a serious potential for life-threatening adverse effects from the reprocessing and reuse of disposable dialysis devices. These throw-away devices include the dialyzer, blood lines, transducer filter and the plastic dialyzer caps. For example, I was shocked to learn that the deaths of at least 14 patients within a six month period in two dialysis clinics in the same city may have been caused by bacterial infection from faulty reprocessing.

I was equally distressed to learn that as many as 60% of the estimated 75,000 patients dialyzed in this nation's 1,200 dialysis clinics and centers are being exposed to cancer-causing formaldehyde as their dialysis devices are reprocessed and reused. Formaldehyde, which is used to "sterilize" the disposable devices for reuse, leaches out directly into the patient's blood as it passes through the dialyzer filter. Surely, there must be a better way to treat these very sick patients who depend on dialysis for their very survival.

Therefore, I would very much appreciate your addressing the following questions in regards to HCFA's efforts to protect the rights and safety of dialysis patients in the ESRD program:

1. Has HCFA, as funder and manager of the ESRD program, determined whether the reuse of disposable dialysis devices, including dialyzers, blood lines, transducer filters and dialyzer caps, is safe and efficacious under existing clinical practices?

Honorable Henry R. Desmarais, M.D.
February 21, 1986
Page 2

2. Is there a need for further study, preclinical and/or clinical, in order to determine whether there are injurious and/or life-threatening acute, short term and/or long term effects associated with the reprocessing and reuse of disposable dialysis devices?

3. Should there be informed consent and freedom of choice for dialysis patients who are requested by clinicians to reuse disposable dialysis devices?

4. Should there be uniform federal standards for the reprocessing and reuse of disposable dialysis devices?

5. Should all dialysis clinics and centers be required to reuse disposable dialysis devices in order to reduce costs in the ESRD program?

6. What has been HCFA's policy over the past decade regarding informed consent and freedom of choice for patients who may be asked to reuse their disposable dialysis devices? Has this policy changed during this period and, if so, what was the substance of each of these changes?

7. What has been HCFA's policy over the past ten years regarding dialysis clinics and centers that may insist on their patients submitting to reuse of their disposable dialysis devices? Has this policy changed during this period and, if so, what was the substance of each of these changes?

The hearing is scheduled to begin at 9:30 a.m. on March 6, 1986 in room SD-628 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with ten copies of your testimony by close of business on March 3, 1986, and an additional 100 copies on the morning of March 5, 1986. Your testimony for submission into the record may be whatever length you deem appropriate. The Committee would, however, appreciate your limiting your oral remarks to no more than five minutes.

Should you have any questions regarding the hearing, please have your staff contact James Michie or David Cunningham of the Committee staff at 224-5364.

Thank you for your cooperation and assistance.

Sincerely,

John Heinz
Chairman

JH:jfm

JOHN HEINZ, PENNSYLVANIA, CHAIRMAN

WILLIAM S. COHEN, MAINE
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DIANE LIFSEY, MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510

February 21, 1986

Honorable Frank Young, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, Md. 20857

Dear Dr. Young:

As Chairman of the Special Committee on Aging, I am writing to request that you appear before the Committee on the morning of March 6, 1986 to provide testimony on the Food and Drug Administration's policy in ensuring safety and efficacy in the reprocessing and reuse of disposable hemodialysis devices.

A four-month Committee staff investigation has revealed a serious potential for life-threatening adverse effects from the reprocessing and reuse of disposable dialysis devices. These throw-away devices include the dialyzer, blood lines, transducer filter and the plastic dialyzer caps. For example, I was shocked to learn that the deaths of at least 14 patients within a six month period in two dialysis clinics in the same city may have been caused by bacterial infection from faulty reprocessing.

I was equally distressed to learn that as many as 60% of the estimated 75,000 patients dialyzed in this nation's 1,200 dialysis clinics and centers are being exposed to cancer-causing formaldehyde as their dialysis devices are reprocessed and reused. Formaldehyde, which is used to "sterilize" the disposable devices for reuse, leaches out directly into the patient's blood as it passes through the dialyzer filter. Surely, there must be a better way to treat these very sick patients who depend on dialysis for their very survival.

Therefore, I would very much appreciate your addressing the following questions in regards to the FDA's responsibilities to ensure safety and efficacy in the use of these disposable devices:

1. Is the reuse of disposable dialysis devices, including dialyzers, blood lines, transducer filters and dialyzer caps, safe and efficacious under existing clinical practices?

2. Is there a need for further study, preclinical and/or clinical, in order to determine whether there are injurious

Honorable Frank Young, M.D.
February 21, 1986
Page 2

and/or life-threatening acute, short term and/or long term effects associated with the reprocessing and reuse of disposable dialysis devices?

3. Should there be informed consent and freedom of choice for dialysis patients who are requested by clinicians to reuse disposable dialysis devices?

4. Should there be uniform federal standards for the reprocessing and reuse of disposable dialysis devices?

5. Should all dialysis clinics and centers be required to reuse disposable dialysis devices in order to reduce costs in the end stage renal disease (ESRD) program?

6. What has been the FDA's policy since 1976, when Congress mandated the regulation of medical devices, on ensuring safety and efficacy in the reprocessing and reuse of disposable dialysis devices? Has this policy changed over the past decade and, if so, in what respects?

The hearing is scheduled to begin at 9:[illegible] a.m. [illegible] March 6, 1986 in room SD-628 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with ten copies of your testimony by close of business on March 3, 1986, and an additional 100 copies on the morning of March 5, 1986. Your testimony for submission into the record may be whatever length you deem appropriate. The Committee would, however, appreciate your limiting your oral remarks to no more than five minutes.

Should you have any questions regarding the hearing, please have your staff contact James Michie or David Cunningham of the Committee staff at 224-53[illegible]4.

Thank you for your cooperation and assistance.

Sincerely,

John Heinz
Chairman

JH:jfm

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the Secretary

Washington, D.C. 20201

February 28, 1986

The Honorable John Heinz
Chairman
Special Committee on Aging
Washington, D.C. 20510

Dear Mr. Chairman:

This is in response to your February 21 letters of invitation to the Acting Administrator of the Health Care Financing Administration (HCFA) and the Commissioner of the Food and Drug Administration (FDA) to appear before the Committee on March 6 to testify on reprocessing and reuse of disposable hemodialysis devices.

We are pleased to accept your invitation. John Marshall, Ph.D., Director of the National Center for Health Services Research and Health Care Technology Assessment will represent the Public Health Service. He will be accompanied by John C. Villforth, Director of the Center for Devices and Radiological Health, Food and Drug Administration. Bartlett S. Fleming, Acting Deputy Administrator, HCFA, will represent that agency and will be accompanied by Charles Booth, Director of the Office of Reimbursement Policy.

As we have expressed to your staff director, we would have preferred that this hearing be scheduled at a later date due to the complexity of the issue and the need for internal coordination. Nevertheless, we will make every attempt to provide you with copies of the testimony as soon as they become available.

Sincerely,

Lawrence J. DeNardis
Acting Assistant Secretary
for Legislation

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing Administration

Washington, D.C. 20201

JUN 13 1986

JFM

The Honorable John Heinz
United States Senate
Washington, D.C. 20510

Dear Senator Heinz:

This letter is to inform you of the actions taken by the Health Care Financing Administration (HCFA) relative to the first panel of witnesses who testified at your March 6, 1986 dialyzer reuse hearing. As you recall, I promised that we would investigate the specific concerns and issues raised by Melinda McFadden and Vagn Vogter. Both Ms. McFadden, a dialysis patient at Bio-Medical Applications, Inc. (BMA) of Central Philadelphia, and Mr. Vogter, a dialysis patient at South St. Petersburg (Florida) Artificial Kidney Center, expressed concern that their respective dialysis centers had forced them to reuse disposable hemodialysis devices.

We are pleased to report that Ms. McFadden's case appears to have been resolved. Staff from our Philadelphia regional office telephoned Ms. McFadden on April 22, 1986 and again for follow-up on May 2, 1986. In both instances Ms. McFadden reported that she was doing well and that improvements regarding patients' rights had been made at her dialysis facility. In the April 22 telephone interview, Ms. McFadden specifically reported that the center has a new patient Bill of Rights, that patients are being informed about BMA's grievance procedures, that the center maintains informed consent policies and, lastly, that the center will notify patients about any national information concerning their care and services. In the follow-up conversation of May 2, Ms. McFadden continued to state that she was doing well and that her spirits were up. She also reported that the center is providing more information to patients and is explaining medical procedures about dialysis.

Mr. Vogter's case is presently being dealt with by our Atlanta regional office. Staff from this office had previously scheduled a Federal monitoring survey at South St. Petersburg Artificial Kidney Center during the early part of June 1986. During this visit, they will investigate Mr. Vogter's case. I will report to you the results of this investigation when they become available to us.

The other two witnesses, Robert Rosen, a dialysis patient and Chairman of the National Kidney Patients Association, and Malcolm Shuman, surviving son of former Baton Rouge dialysis patient, Elaine Menville Shuman, did not voice specific concerns at the March 6th hearing which required follow-up HCFA investigation. For your information, however, a complaint investigation was conducted at BMA of Central Philadelphia on December 27 and 30, 1985 in response to allegations which Mr. Rosen previously shared with HCFA's Philadelphia regional office. This investigation revealed one Federal deficiency concerning the center's official policy and procedure manual not including a segment on the rules and regulations governing patient responsibilities and conduct.

The deficiency was subsequently corrected in a timely fashion by the facility's administrator. Mr. Rosen's other allegations regarding patient care and services, patient rights and grievance procedures, the physical environment of the center, and patient clinical records were not found to be deficient in the December investigation.

At the March 6, 1986 hearing Malcolm Shuman discussed his Mother's care at the BMA dialysis facility in Baton Rouge, Louisiana. As you are aware, in 1982 an outbreak of nontubercular mycobacterial infection was reported at this facility which infected 140 patients, 14 of whom subsequently died. A Centers for Disease Control (CDC) investigation of this case found the cause of the outbreak to be water contamination by mycobacteria. A December 6, 1985 Dallas regional office survey of this facility indicated favorable compliance with no major deficiencies in Federal regulations noted. Furthermore, the facility, which practices reuse, maintains grievance procedures and informed consent policies for all patients.

Though HCFA's policy has always been that the decision to reuse is a medical practice issue, which should be decided by a patient's physician, we do not, and will not, tolerate facilities which "force" their patients to reuse at the risk of being denied treatment. We will continue to monitor ESRD facilities as part of our survey and certification process and will investigate all patient complaints.

We hope you find this information helpful. If I can be of any additional assistance, please do not hesitate to contact me.

Sincerely,

Bartlett A Fleming

Bartlett S. Fleming
Associate Administrator for
Management and Support Services

Item 6

Documents From Federal And State Agencies And Private Organizations Pertaining To The Reuse Of Dialysis Devices

11/11/77	FDA Compliance Policy Guide 7124.23, Chapter 24 - Devices. SUBJECT: Reuse of Medical Disposable Devices.
10/20/78	Memo to Administrator, HCFA, from Asst. Secretary for Health and Surgeon General. RE: Coordination of a Work Plan for Studies on End-Stage Renal Disease (ESRD) - INFORMATION.
1/15/79	Memo to Asst. Secretary for Health and Surgeon General from Administrator, HCFA. RE: Coordination of Experiments and Studies on ESRD Authorized by P.L. 95-292; Your memo of Oct. 20 [1978].
5/20/79	"DIALYZER REUSE: [National Association of Patients on Hemodialysis and Transplantation, Inc.]'s Statement of Position" position paper adopted by the Board of Directors of the National Association of Patients on Hemodialysis and Transplantation, Inc.
2/25/80	Memo to Helen Smits, Director, Health Standards and Quality Bureau (HSQB), HCFA, from Nancy Cummings, M.D., Director, Kidney, Urologic and Blood Diseases Program, NIAMDD, NIH. RE: Research in relation to ESRD/Chronic Renal Failure.
1/5/81	Memo to the Assistant Secretary for Health, DHHS, from Jere Goyan, M.D., FDA Commissioner. RE: reuse of dialyzers--a response to 11/18/80 ASH inquiry about reuse.
1/7/81	Letter to E. L. Kelly, Acting Director, Office of Special Programs, HCFA, from Nancy B. Cummings, M.D., Associate Director, National Institute of Arthritis Metabolism and Digestive Diseases (NIAMDD), National Institutes of Health (NIH), and Robert Wineman, Ph.D., Program Director, Chronic Renal Disease Program, NIAMDD, NIH. RE: research and/or demonstrations relating to ESRD.
1/15/81	Memo to Dr. Nancy Cummings, Director, NIAMDD, NIH, and James Kaple, Director, Office of Research and Development Standards (ORDS), HCFA, from Ronald Schwartz, Acting Assistant Inspector General (IG) for Health Care and Systems Review. RE: Request for Information on Kidney Dialyzer Reuse Research.
1/28/81	Memo to Acting Assistant IG, Health Care and Systems Review, DHHS, from Nancy Cummings, M.D., Associate Director, NIAMDD, NIH. RE: Telephone Conversation (1/28/81) about Dialyzer Reuse memo which was never received.

2/81	Memo to R. D. Schwartz, Acting Assistant IG for Health Care & Systems Review, from James Kaple, Acting Director, Office of Research, Demonstrations and Statistics, HCFA. RE: Response to Your Request For Information Pertaining to Kidney Dialyzer Reuse.
4/2/81	Memo to Ronald Schwartz, Acting Assistant IG for Health Care & Systems Review, DHHS, from Acting Director, Bureau of Medical Devices, FDA. RE: response to Schwartz 2/25/81 memo on dialyzer reuse.
4/9/81	Memo to Nancy Cummings, M.D., Director, Kidney, Urologic and Blood Disease Program, NIH, from Edward Kelly, Acting Director, Office of Special Programs, HCFA. RE: multiple use of dialyzers.
4/15/81	Letter to Dr. Seymour Perry, Director, National Center for Health Care Technology, DHHS, from Robert Wineman, Ph.D., Program Director, Chronic Renal Disease Program, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDKD), NIH. RE: Comments on the ESRD Program Evaluation Plan.
4/23/81	Letter to Norman Deane, M.D., National Nephrology Foundation (NNF), from John Ketteringham, Ph.D., Vice President, Arthur D. Little Inc. (ADL) RE: Ketteringham's request to review the report on the NIH funded study prior to publication.
5/4/81	Letter to John Ketteringham, Ph.D., Arthur D. Little Inc., from Norman Deane, M.D., National Nephrology Foundation, Manhattan Kidney Center. RE: response to Dr. Ketteringham's 4/23/81 letter.
5/6/81	Memo to Edward Kelly, Acting Director, Office of Special Programs, HCFA, from Nancy Cummings, M.D., Associate Director, KUBD/NIADDK, NIH. RE: reuse of dialyzers--response to Kelly's 4/9/81 memo.
5/21/81	Memo to Stuart Nightingale, M.D., Acting Associate Commissioner for Health Affairs, FDA, from F. Villarroel, Director, Division of Gastroenterology-Urology and General Use Devices, Bureau of Medical Devices, FDA. RE: reuse of dialyzers.
7/1/81	FDA Compliance Policy Guide 7124.16, Chapter 24 - Devices. SUBJECT: Reuse of Medical Disposable Devices.
7/31/81	Memo to Carolyn Davis, Administrator, HCFA, from Edward Kelly, Acting Dir., Office of Special Programs, HCFA. RE: dialyzer reuse.
8/11/81	Note to Drs. Rubin and Brandt, Assistant Secretary for Health, DHHS, from Carolyn Davis, Administrator, HCFA. RE: dialyzer reuse.

10/7/81	Memo to William Ketterer, DHHS General Counsel, from Harvard Gregory, Contracting Officer, NIADDK, NIH. RE: Telephone Conversation concerning the National Nephrology Foundation Contract with subcontractor Arthur D. Little, Inc. (ADL).
10/9/81	Letter to Norman Deane, M.D., National Nephrology Foundation, Inc. (NNF), from John Ketteringham, Ph.D., Vice President, Arthur D. Little, Inc. RE: Contract No. NO1-AM-9-2214.
11/18/81	Letter to Michael J. Miller, Executive Director, Association for the Advancement of Medical Instrumentation (AAMI), from Nancy Cummings, M.D., Associate Director, Kidney, Urologic, and Hematologic Diseases, NIADDKD, NIH. RE: conference on reuse of hemodialyzers.
2/18/82	Memo to Secretary, DHHS, from James Donovan, M.D., Chairman, ESRD Strategic Work Group (organized by HCFA and included managers from DHHS, HCFA and NIH--22 members in all). RE: Chairman's Report--INFORMATION.
3/15/82	Letter to Robert Wineman, M.D., NIH, from John Ketteringham, Ph.D., Vice President, Arthur D. Little Inc. RE: "amended version" of the report, "Multiple Use of Hemodialyzers".
3/19/82	Letter to John Ketteringham, Ph.D., Vice President, Arthur D. Little Inc. (ADL), from Robert Wineman, Ph.D., Program Director, Chronic Renal Disease Program, NIADDKD, NIH. RE: response to Dr. Ketteringham's letter of 3/15/82.
7/29/82	Letter to the DHHS Public Health Service from Robert Rosen, dialysis patient. RE: a Freedom of Information request for policy statement on reuse of dialysis devices.
9/20/82	Letter to Mr. Reynolds, Food and Drug Administration, from Robert Rosen, dialysis patient. RE: Freedom of Information request concerning the safety of reusing dialyzers that have been rinsed out with a formaldehyde solution.
9/21/82	Letter to Robert Rosen, dialysis patient, Bensalem, Pa., from John Newmann, President of the National Association of Patients on Hemodialysis and Transplantation, Inc. (NAPHT). RE: Napht's opposition to reuse of dialysis devices.
10/22/82	Letter to Robert Rosen, dialysis patient, from F. Villarroel, Ph.D, Director, Division of Gastroenterology-Urology and General Use Devices, Office of Medical Devices, CDRH, FDA. RE: formaldehyde in dialyzer reuse.
12/7/82	Letter to James Rhoades, Pa. Senate, from John Villforth, Director, Center for Devices and Radiological Health, FDA. RE: response to Rhoades' 11/1/82 letter.

12/?/82	Letter (undated) to U.S. Representative James Coyne, 8th District of Pa., from Carolyne Davis, Administrator, HCFA. RE: response to Coyne letter to Secretary Schweiker concerning Robert Rosen, dialysis patient.
12/13/82	Memo to Edward Brandt, M.D. Jr., Assistant Secretary for Health, DHHS, from Arthur Hayes, Jr., M.D., Commissioner, FDA. RE: FDA's involvement in reuse of dialyzer equipment.
12/14/82	Memo to the Executive Secretary, DHHS, from Dale Sopper, Assistant Secretary for Management and Budget, DHHS. RE: Report of the Intradepartmental Work Group on ESRD.
12/14/82	Letter to Robert Rosen, dialysis patient, from U.S. Rep. James Coyne, 8th Dist., Pa. RE: HCFA response to Coyne letter.
1/6/83	Letter to Robert Rosen, dialysis patient, from Larry Oday, Director, Bureau of Program Policy, HCFA. RE: response to a Rosen letter.
1/6/83	Letter to Sen. Arlen Specter of Pa. from Larry Oday, Director, Bureau of Program Policy, HCFA. RE: Robert Rosen, dialysis patient.
2/11/83	Memo to Agency Heads, Office of Assistant Secretary for Health Staff Officers, from Edward Brandt, Jr., M.D., Assistant Secretary for Health, DHHS. RE: End-Stage Renal Disease.
3/15/83	Letter to Sen. Arlen Specter of Pa. from Robert Wetherell, Associate Commissioner, FDA. RE: response to Specter's 2/18/83 letter concerning Robert Rosen, dialysis patient.
5/11/83	42 CFR Part 405. "Medicare Program; End-Stage Renal Disease Program; Prospective Reimbursement for Dialysis Services and Approval of Special Purpose Renal Dialysis Facilities; Final Rule", HCFA, DHHS, Fed. Reg. p. 21272, Vol. 48, No. 92.
7/6/83	Memo to Assistant Director, Education and Communication, CDRH, FDA, from Mark Barnett, Director, CDRH, FDA. RE: Meeting of CDRH working group on dialyzer reuse, July 1, 1983.
8/23/83	Letter to Robert Rosen, dialysis patient, from J. D. Sconce, Administrator, Region VI, HCFA. RE: Rosen's questions concerning deaths of 13 dialysis patients in Baton Rouge, Louisiana.
8/30/83	Minutes (dated 9/7/83) of first meeting of Reuse Committee, FDA, by Lawrence Kobren, Chairperson.
10/3/83	Minutes of meeting of the Reuse Committee, FDA, by L. Kobren.

10/5/83	Memo to the Assistant Secretary for Health, DHHS, from Lester Salans, M.D., Director, NIADDKD, NIH, and Chairman, Public Health Service Coordinating Committee for ESRD. RE: Report of Committee.
11/9/83	Minutes of meeting of the Reuse Committee, FDA, by L. Kobren.
11/30/83	FDA "Dear Doctor" letter. RE: requirements for appropriate rinsing of new dialyzers to avoid severe hypersensitivity reactions with new dialyzers.
12/5/83	Minutes of the first meeting of the Association for the Advancement of Medical Instrumentation's (AMMI) Reuse Committee, Washington, D.C.
1/25/84	Minutes of a meeting of the Reuse Committee, FDA, by (unsigned).
3/28/84	"Notes" of AAMI Reuse Subcommittee meeting, Washington, D.C.
4/12/84	Letter to Robert Taylor, Associate Administrator, Division of Health, Standards and Quality, Region III, HCFA, from Frances Bowie, Service Facility Regulation Administration, Department of Consumer and Regulatory Affairs, D.C. Government. RE: referral to HCFA of complaint received by Bowie concerning reuse of dialysis devices.
4/[illegible]/84	Minutes of a meeting of the Reuse Committee, FDA, by L. Kobren.
4/19/84	Letter to J. Kevin Rooney, Atty., from Walter Gundaker, Director, Office of Compliance, CDRH, FDA. Re: response to Rooney's 3/9/84 letter concerning reuse.
4/20/84	Letter to R. E. Easterling, M.D., chairman, AAMI Reuse Subcommittee, from M. S. Favero, Ph.D., Centers for Disease Control (CDC). RE: rationale for justification of using 4% formaldehyde solution in reprocessing dialysis devices.
5/4/84	Minutes of an AAMI Reuse Subcommittee meeting, Washington, D.C.
5/10/84	Minutes of a meeting of the Reuse Committee, FDA, by (unsigned).
7/3/84	Memo to Patricia Harfst, Director, Division of Institutional and Ambulatory Services, Office of Survey and Certification, Health Services Quality Bureau, HCFA HQ., from Claudette Campbell, Acting Chief, Survey and Certification Review Branch, Region III Office, HCFA. RE: complaints from D.C. state survey agency concerning reuse of blood lines in a dialysis center.

7/3/84	Memo to General Counsel, FDA, from John Villforth, Director, Center for Devices and Radiological Health (CDRH), FDA. RE: Request for Legal Opinion of the Applicability of Section 21 CFR 801.4 the to reuse of dialysis devices.
7/18/84	Regulations of the Colorado Department of Health: Single Use Disposable Medical Devices. RE: Reuse of dialyzers.
8/1/84	Letter to Robert Rosen, dialysis patient, from John Villforth, Director, Center for Devices and Radiological Health (CDRH), FDA. RE: response to Rosen's 5/31/84 letter addressed to President Reagan and concerning reuse of dialyzers.
8/6/84	Letter to John Villforth, Director, CDRH, FDA, from Robert Rosen, dialysis patient. RE: reuse of dialysis devices.
8/10/84	Memo to Director, Office of Survey and Certification, HSQB, HCFA, from Robert Streimer, Director, Office of Coverage Policy, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: Policy Guidance Regarding the Reuse of Disposables for Renal Dialysis .
8/17/84	Letter to Robert Rosen, dialysis patient, from Don Nicholson, Assistant I.G., DHHS. RE: response to Rosen's 5/31/84 letter on reuse of dialyzers.
8/20/84	Letter to Perry Ecksel, National Kidney Patient's Association, Philadelphia, Pa., from Senator Edward M. Kennedy. RE: response to Ecksel concerning reuse.
8/22/84	Minutes of a AAMI Reuse Subcommittee meeting in Chicago, Ill.
8/27/84	Letter to Perry Ecksel, National Kidney Patients Association, Philadelphia, Pa., from Henry Desmarais, M.D., Director, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's inquiry on reuse of dialyzers.
9/10/84	Letter to Sen. Arlen Specter, Pa., from Robert Wetherell, Associate Commissioner, FDA. RE: response to Sen. Specter's 7/18/84 request concerning Robert Rosen, dialysis patient.
9/12/84	Letter to Robert Rosen, dialysis patient, from John Villforth, Director, Center for Devices and Radiological Health, FDA. RE: response to Rosen's 8/6/84 letter.
9/17/84	Letter to Robert Rosen, dialysis patient, from Lawrence Kobren, Chairman, Reuse Committee, CDRH, FDA. RE: response to Rosen's 7/25/84 letter.

9/25/84	Memo to John Villforth, Director, CDRH, FDA, from Ann Witt, Office of General Counsel, FDA. RE: Reuse of Medical Devices; Adequate Directions for Use.
9/28/84	Letter to Perry Ecksel, National Kidney Patients Association, Philadelphia, Pa., from Henry Demarais, M.D., Director, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's inquiries.
12/7/84	Minutes of an AAMI Reuse Subcommittee meeting, Washington, D.C.
12/31/84	Letter to Perry Ecksel, National Kidney Patients Association, Philadelphia, Pa., from Edward Brandt, Jr., M.D., Assistant Secretary for Health, DHHS. RE: Response to Ecksel's 10/30/84 letter to Secretary Heckler concerning reuse of dialyzers.
3/5/85	Letter to Carolyne Davis, Administrator, HCFA, from U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, Committee on Ways and Means. RE: concerns about reuse of dialyzers.
3/5/85	Letter to Frank Young, M.D., Commissioner, FDA, from U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, House Committee on Ways and Means.
3/14/85	Minutes of a meeting of the Reuse Committee, FDA, by Nancy Clements.
4/8/85	Letter to Elizabeth Bridgman, Manager, Technical Development, AAMI, from M. Favero, M.D., CDC. RE: quality of water used in the reprocessing of dialysis devices.
4/10/85	Letter to U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, House Committee on Ways and Means, from Carolyne Davis, Administrator, HCFA. RE: response to Stark's 3/5/85 letter.
4/24/85	Minutes of a meeting of the Reuse Committee, FDA, by (unsigned).
4/26/85	Regional (HCFA Region VI) Health Standards and Quality Letter No. 85-13 To All State Survey Agencies and All Title XIX Single State Agencies. RE: Reuse of Single-Use and Disposable Medical Equipment in ESRD Facilities.
4/30/85	Minutes of an AAMI Reuse Subcommittee meeting in Atlanta, Ga.
5/21/85	Memo to Gordon Oxborrow, Minneapolis Center for Microbiological Investigation, FDA, from James J. Park, CDRH, FDA. RE: Request for study of formaldehyde and glutaraldehyde toxicity in the blood.

7/2/85	Memo to Reuse PMS (Program Management Staff) & OTS Reuse WG (working group), CDRH, FDA, from L. Kobren, OTA-DTD, CDRH, FDA. RE: Plan of Action--Reuse Policy.
7/3/85	Letter to Perry Ecksel, Kidney Patients Association, Philadelphia, Pa., from Robert Wren, Director, Office of Coverage Policy, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's recent letter about coverage and reimbursement for reprocessed devices.
7/18/85	Interoffice Memorandum to the Reuse PMS and OTA Reuse WG, DHHS, from L. Kobren RE: Reuse Minutes.
8/8/85	Interoffice Memorandum to the Reuse PMS & OTA Reuse WG, from Kobren. RE: Reuse Committee minutes.
10/3/85	Letter to Robert Taylor, Associate Regional Administrator, Division of Health Standards and Quality, Region III, HCFA, from Frances Bowie, Service Facility Regulation Administration, Department of Consumer and Regulatory Affairs, D.C. Government. RE: the need for clear guidelines from HCFA on reuse.
10/25/85	Speech by John Villforth, Director, CDRH, FDA, at the Georgetown University annual conference on reuse of disposable medical devices. RE: Reuse Of Disposable Medical Devices: Regulatory Considerations.
Nov. 1985	"The Journal Of Infectious Diseases", Vol. 152, No. 5, included the CDC report of 6/24/85, "Infections with Mycobacterium chelonei in Patients Receiving Dialysis and Using Processed Hemodialyzers".
11/18/85	Letter to Frances Bowie, Service Facility Regulation Administration, Department of Consumer and Regulatory Affairs, D. C. Government, from Claudette Campbell, Chief, Survey and Certification Review Branch, Region III Office, HCFA. RE: response to Bowie's 10/3/85 letter concerning HCFA position on reuse of dialyzers and bloodlines.
11/19/85	Letter to Pa. Governor Thornburgh from Perry Ecksel, National Kidney Patients Association, Feasterville, Pa. RE: Re-use of Medical Disposables.
12/4/85	Letter to Perry Ecksel from Robert Streimer, Acting Director, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: letters to the Secretary of DHHS on reuse.
12/4/85	Letter to AAMI from John Villforth, Director, CDRH, FDA. RE: FDA representatives for participation in AAMI's standards development committees.
2/24/86	"Working Paper: Policy Considerations For The Reprocessing Of Devices", by the Reuse Committee, Center for Devices and Radiological Health, FDA.
7/8/86	Memo to Asst. Secretary for Health from John Marshall PH.D., Dir., National Center for Health Science Research and Health Care Technology. Re: NCHSR assessment on reuse and the need to take a position counter to that presented in testimony at the Aging Committee's March 6, hearing.

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDES

GUIDE 7124.23

CHAPTER 24 - DEVICES

SUBJECT: Reuse of Medical Disposable Devices

BACKGROUND:

Investigations by the Food and Drug Administration (FDA) and other Federal agencies have disclosed that a number of health care institutions have engaged in the practice of reusing single use sterile disposalbe medical devices. Such devices may not be amenable to resterilization and/or reuse. The FDA is not aware of any data which would establish conditions for the safe and effective cleaning and subsequent resterilization and/or reuse of any disposable medical devices.

In January of 1975, the Bureau of Health Insurance of the Social Security Administration issued State Agency Letter No. 29 concerning the Reuse of Disposable Guidewires and Catheters. The letter stated that such devices were not to be reused. Since that time, the FDA has received a number of inquiries relative to the economics of its policy as related to issues concerning protection of the public health, and has been requested to reconsider and reevaluate the position it has taken.

The FDA, in recognition of the validity of the concerns expressed by all parties involved in this matter has reviewed its position on this issue, but finds that there is a lack of data to support the general reuse of disposable medical devices, including disposable guidewires and catheters. The fact that disposable devices are labeled disposable is indicative of this lack of data. In order for a device to be considered "reusable," it must be capable of withstanding necessary cleaning, and resterilization techniques and methods, and continue to be safe and reliable for its intended use.

The FDA has concluded, therefore, that the institution or practitioner who reuses a disposable medical device should be able to demonstrate: (1) that the device can be adequately cleaned and sterilized, (2) that the physical characteristics or quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use. Moreover, since disposable devices are not intended by the manufacturer or distributor for reuse, any institution or practitioner who resterilizes and/or reuses a disposable medical device must bear full responsibility for its safety and effectiveness.

POLICY:

The Food and Drug Administration considers disposable devices which are being reused, and which have not been demonstrated to be capable of complying with the requirements in the above paragraph, to be adulterated within the meaning of 21 U.S.C. 351(a)(2)(A) and in violation of 21 U.S.C. 331(k).

ANDUM

OFFICE OF THE ASS SECRET [redacted]

Attachment 1(9)

DATE: OCT 2 0 1978

Administrator
Health Care Financing Administration

OM : Assistant Secretary for Health and
Surgeon General

JECT: Coordination of a Work Plan for Studies on End-State Renal Disease
(ESRD) - INFORMATION

This is in response to your memo of September 8 in which you suggest developing a joint work plan for studies of ESRD, as outlined in P.L. 95-292.

Since the governmental financial coverage of ESRD will reach $1 billion by 1980, studies listed, in P.L. 95-292, for ESRD should be started or evaluated quickly. Included are a variety of studies regarding the more efficient use of equipment, reimbursement of physicians and other health professionals, and the potential of other treatment modalities (e.g., dietary control, transplantation). Studies with respect to the prevention and cure of kidney disease would appear to have the greatest potential for cost savings.

A joint effort between PHS/HCFA for a work plan in prevention, treatment, technology, and financing of ESRD is an excellent idea. The involved agencies should include:

Research:
1. Kidney, Urologic and Blood Disease program NIAMDD (Dr. Nancy B. Cummings)
2. Artificial Kidney-Chronic Uremia program, NIAMDD (Dr. Benjamin Burton)

Dialyzer Reuse:
1. FDA
2. Technology Assessment Agencies
3. OST

Financial Policy and Coverage:
1. OHPRS - Joseph Eichenholz
Dr. Leah M. Lowenstein
2. HCFA

The Public Health Service (PHS) expects to be reimbursed by HCFA for all research performed by PHS in this regard. In response to a note dated September 15 from Kathy Buto, the Deputy Executive Officer, PHS concurred with projected funding estimates developed by the FDA and NIH.

Page 2 - Administrator, HCFA

This coordinating committee should be formed speedily. Our office would be happy to assume the role of coordinator.

Julius B. Richmond
Julius B. Richmond, M.D.

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EMORANDUM

DEPARTMENT OF HEALTH [redacted]
HEALTH CARE FIN.

Attachment 2

DATE: JAN 15 1979

TO: Assistant Secretary for Health and
Surgeon General

OM : Administrator, HCFA

BJECT: Coordination of Experiments and Studies on ESRD Authorized by
P.L. 95-292; Your Memorandum of October 20

In response to your October 20 memorandum, we agree that a coordinating committee consisting of HCFA and PHS representatives would be an appropriate mechanism for developing a joint work plan to address the studies and experiments mandated in P.L. 95-292. This committee should be jointly chaired by HCFA and PHS and should include all relevant components of the two agencies. As you pointed out in your memorandum, these projects will need to be initiated soon. Please have your staff contact Jane Fullarton of the Office of Policy, Planning and Research, HCFA, at (202) 245-0697 about organizing a committee.

With respect to research costs, we expect that the costs of administering and evaluating the studies and experiments will be funded by the respective agencies with lead responsibility, as outlined in our memorandum of September 8. HCFA is planning to request a supplemental appropriation to cover the necessary costs of carrying out studies and experiments in the following areas:

Dialysis equipment
Home dialysis aides and other methods of reducing ESRD program costs
Study of physician reimbursement
Study of non-Medicare entitled ESRD patients
Cost analysis of dialyzer reuse

We expect the Public Health Service to arrange for obtaining funds to conduct studies of dietary control methods, organ donation programs, and the medical appropriateness of dialyzer reuse. We would like to point out, however, that it may be possible to obtain Medicare waivers to pay for patient service costs relative to dietary control methods, or other experiment-related services that are not currently Medicare-covered. This option can be explored further by the interagency coordinating committee.

Leonard Schaeffer

DIALYZER REUSE

Napht's Statement of Position

NAPHT is opposed to the reuse of disposable hemodialysis filters at the present time except in carefully planned and controlled experimental situations where patients elect to participate in the study.

Although current data indicate that small molecules such as urea or creatinine are removed as well with reused as with new hemodialyzers, similar data are not available for removal of larger (or "middle") molecules. One report indicated a significant decrease in the removal of those molecules after hollow fiber dialyzers were sterilized with formaldehyde after only one use. Also lacking is a reasonable scientific assessment of the possible immunological consequences of exposing patients to blood cellular and protein elements remaining in dialyzers that have been prepared for reuse.

Hemodialyzers are marketed for one time use only as indicated on their labels. Good manufacturing practices and Food and Drug Administration regulations require careful and standardized testing of these devices for sterility, pyrogenicity, biocompatibility and product performance. Nevertheless, there are known side effects such as pyrogenic reactions or infection which occur during dialysis with first time use. Inadequate controls on the reprocessing of hemodialyzers for reuse by a variety of institutions and personnel may increase the incidence of these side effects in treatment with reused dialyzers.

Dialysis patients are concerned not only that they remain alive but that the quality of their lives be as good as possible. Any medical device or procedure that may reduce either the length or quality of their lives is therefore viewed with great concern. While we recognize that the medical data are not all known on the issue of dialyzer reuse (as on other issues), we are concerned that patients be fully informed about their therapy and that they have full freedom of choice on this issue.

The patient being asked to reuse dialyzers should be informed of the possible side effects, of expected number of uses, and of the methods and controls on reprocessing. The patient should consent to treatment with reused dialyzers prior to being so treated and should have the discretion to discontinue reuse at any time. This is particularly relevant to the approximately 17% of units currently practicing reuse.

While NAPHT strongly supports and encourages attempts to lower dialysis treatment costs, we are firmly opposed to doing so by increasing the medical risks to patients. At the current time, we do not believe sufficient data exist to show that dialyzer reuse does not increase those risks in either the short or long term. We encourage further research and study in this area, and we welcome further discussion on this issue. We particularly solicit specific instances of satisfactory or unsatisfactory experience with dialyzer reuse.

Until such time as dialyzer reuse is proven to be safe and effective (by careful scientific study as well as by clinical observation), NAPHT is opposed to this practice.

(Adopted by the Board of Directors of the
National Association of Patients on
Hemodialysis and Transplantation, Inc.
May 20, 1979)

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Statement by Dr. Eli A. Friedman,
Medical Advisor to NAPHT:

Dialyzer reuse involves real risk to the patient when performed improperly. Incomplete studies indicate that even properly treated hollow fiber dialyzers may have reduced efficiency in middle molecule extraction when reused. NAPHT's concern for the patient exposed to a reused dialyzer is genuine and understandable. Exactly how and under what circumstances patients should be exposed to repetitive use of the same dialyzer is a reasonable subject for clinical investigation. Until convincing data is in hand, I concur with NAPHT's views that dialyzer reuse be viewed as an experimental undertaking requiring informed patient consent. The apparently "safe" long-term experience of the Seattle group and others in dialyzer reuse for home hemodialysis is noted and recognized. It is hoped that appropriate quantification of these and other experiences will be published to enable the formulation of a complete and fair perspective on this issue which carries important economic and patient safety overtones.

National Association of Patients on Hemodialysis and Transplantation Inc.
505 Northern Boulevard, Great Neck, New York 11021

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

DATE: February 25, 1980

TO : Dr. Helen Smits, Director
Health Standards and Quality Bureau, HCFA

FROM : Director, Kidney, Urologic and
Blood Diseases Program, NIAMDD, NIH

SUBJECT : Research in Relation to ESRD/Chronic Renal Failure

1) Potential research projects which relate primarily to cost-saving techniques and which show little or no projected potential to increase knowledge in fundamental mechanisms of disease or understanding of clinical disorders belong more appropriately to HCFA's purview. For example, the study of dialyzer re-use, mandated in legislation and for which NIH did a one year pilot study, could be justified for HCFA support because of its cost-saving potential. It is unlikely that there are any fundamental or clinical research aspects which would expand or contribute to understanding and treatment of disease in a potential study of dialyzer re-use.

2) NIH-supported research in chronic renal failure places primary emphasis upon increasing understanding of causes and complications of chronic renal failure and upon the potential for new knowledge that would contribute to efforts to prevent, arrest, cure and treat relevant diseases, their complications, and the complications of chronic renal failure.

3) NIH priorities for research support are based upon scientific excellence of proposed studies and not upon economic issues. HCFA-supported research should assess means to provide more cost-effective treatment as well as determination of when to fund new treatment modalities.

4) At the NIH-HCFA research interface might fall the studies of new treatment modalities which have not reached a phase for broad clinical applicability to ESRD patients. If a mechanism is not available for funding new and potentially acceptable therapies, then physicians and surgeons may continue with old therapeutic modalities for economic reasons. It is essential that a means be found to evaluate in a controlled fashion the efficacy of such innovative therapies. Funding by HCFA for such treatment in a limited number of centers where careful control of the treatment (as in a clinical trial) could be exercised and an NIH research grant to assess the validity (or lack thereof) of the treatment modality of high enough quality that the priority assigned by an NIH study section would be in a fundable range might be considered as cooperative undertaking. For example, a careful study between HCFA and NIH of a new immunosuppressive modality for transplantation could be undertaken cooperatively with HCFA funding all patient care costs and NIH funding the data evaluation.

Nancy B. Cummings

Nancy Boucot Cummings, M.D.

Watzman / [illegible] 1/15/81

HFO-1 JAN - 7 REC'D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Attachment #8, DKDC, 11-29-84 LFT.

Memorandum

Date JAN 5 1981

From Commissioner of Food and Drugs

LRS file in subject file under "Hemodialyzers"

Subject Reuse of Hemodialyzers

To Assistant Secretary for Health and Surgeon General
Through: ES/PHS

This is in response to your inquiry of November 18, 1980, about the reuse of hemodialyzers.

The FDA position on the reuse of single use disposable devices also applies to hemodialyzers. The guide is intended to address responsibility for reuse of disposable devices when such action is clearly contrary to the manufacturer's labeling. When an institution or practitioner chooses to reuse a single use hemodialyzer, the responsibility for the safety and effectiveness of the reused device shifts from the manufacturer to the party responsible for the reuse. The enclosed document, "Reuse of Disposable Hemodialyzers," prepared in April 1979, still represents FDA's opinion on this subject--that is, that FDA cannot at this time recommend the reuse of hemodialysis devices.

The studies presently under way at the National Institutes of Health (NIH) will reportedly be concluded in December 1980. These may affect the reuse of hemodialyzers; in the event that the NIH studies change our current position we will advise you. In any case we do not believe there would be any significant change in FDA's position on the question of responsibility under the FD&C Act.

Jere E. Goyan
Jere E. Goyan

Enclosure

CHAP. 24

FYI

☒ RFDD ☒ D D ☒ C B
☒ IB ☒ S B ☒ C A
☒ SBR ☒ MCMI ☒ WEAC
☐ OTHER
FROM: CGB (HFO-420) DATE 1-22-81

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20205

January 7, 1981

Mr. Edward L. Kelly
Acting Director
Office of Special Programs
Health Care Financing Administration
1849 Gwynn Oak Avenue
2B2 Dogwood East
Baltimore, Maryland 21207

Dear Mr. Kelly:

In September we discussed several areas of research and/or demonstrations, which relate to End Stage Kidney Disease. Because of the potentially high economic impact of some of these projects upon future Medicare costs, cooperation between the Health Care Financing Administration (HCFA) and National Institutes of Health (NIAMDD) for both planning and funding of these projects were considered.

It was pointed out in our discussion that the importance to basic science of these projects varied markedly. In some cases the fundamental research contribution to medical science would be fairly low. With this factor in mind, and the general policy of NIH to fund projects based primarily on scientific merit, it would be relatively unlikely that NIH (NIAMDD) would fund some types of research that might have great interest to HCFA because of its economic impact. This situation is especially relevant with restricted budgets and congressional emphasis upon support of basic research by the investigator initiated grant mechanism. For instance NIH (NIAMDD) lacks resources to fund a high proportion of approved, scientifically meritorious research projects.

As you may recall, you suggested several types of mechanisms which could be considered for potential cooperation. These ranged from HCFA's including relevant projects in its research budget, use of exemptions in special cases to pay for patient care costs on a limited demonstration basis, HCFA's administratively establishing uniform guidelines to its intermediaries for payment of patient care costs (required in some multicenter studies), and use of HCFA's staff for data analysis. Further, you asked that we send you examples of projects which might fit your suggested mechanisms and where NIH (NIAMDD) could provide relevant expertise to manage a needed study, use of an interagency agreement could be considered for HCFA's support of part or all of the costs of the proposed study.

These possibilities are best illustrated by specific examples:

(1) Registry for Continuous Ambulatory Peritoneal Dialysis. NIH (NIAMDD) through its contract with the University of Missouri (N01-AM-9-2208)

is in the process of establishing such a registry. NIH plans to operate the registry through an initial period to assist the dialysis community in evaluation of this mode of therapy. For more extended operation, if needed, future transfer of the activity to HCFA's responsibility is in order. Your letter of August 14, 1980 (ELK:NBC) expressed your continued willingness to support this project in principle. Potential cooperation from HCFA: (a) contributions to design of registry, (b) partial funding, and, later (c) direct operation of registry, if continuation is desirable.

(2) Clinical Trial of Multiple Use of Hemodialyzers. NIH (NIAMDD) has funded an initial laboratory study of multiple use of hemodialyzers through a contract with National Nephrology Association (N01-AM-9-2214). To complete the evaluation clinical trials in several centers are required. This is an instance of a research project which is characterized by having a significant economic impact but a low contribution to basic medical science. Potential cooperation from HCFA: (a) Full funding of the needed clinical trials through an interagency agreement with NIH which could conduct the study. (b) Supervision of collection of data on cost and material manpower required for multiple use. (c) Contributions to design of the overall study.

(3) Plasmapheresis for Treatment of Rapidly Progressive Glomerulonephritis. Through a research grant NIH (NIAMDD) has funded a multicenter trial to compare the effect of plasmapheresis and a standardized program of immunosuppression to immunosuppression alone in the treatment of this disease. In contrast to examples 1 and 2, contributions to basic science and to the clinical sphere are anticipated from this study. Potential cooperation from HCFA: Granting of an exemption to regulations so that payment for plasmapheresis and related patient care costs may be made through Medicare, for patients in this or similar well defined, limited scope studies.

Additional details on some of the projects proposed for cooperation are given in appendices 1-6. For the overall generic case of cooperation between HCFA and NIH, other examples beyond those related to ESRD could be added such as heart transplantation, plasmapheresis for treatment of arthritis, etc.

We hope that this information will facilitate your consideration of the generic case, and that action plans might be formulated jointly by HCFA and NIH (NIAMDD) for funding some of the specific projects. We will be glad to supply other information, as well as participate in additional discussions.

Sincerely,

/s/
Nancy B. Cummings, M.D.
Associate Director
Kidney, Urologic, and Blood Diseases
National Institute of Arthritis,
Metabolism, and Digestive Diseases

/s/
Robert J. Wineman, Ph.D.
Program Director
Chronic Renal Disease Program
National Institute of Arthritis,
Metabolism, and Digestive Diseases

Enclosures
Appendices 1-6

15 JAN 1981 OFFICE OF INSPECTOR GENERAL

15 JAN 1981

/s/ Ronald D. Schwartz
Ronald D. Schwartz
Acting Assistant Inspector General
for Health Care and Systems Review

Request for Information on Kidney Dialyzer Reuse Research

See Below

It has come to our attention that the National Institute of Health's (NIH) Institute of Arthritis, Metabolism and Digestive Diseases has discontinued their research efforts into the efficacy and safety of kidney dialyzer reuse.

Under the 1978 Amendments to the Social Security Act, P.L. 95-292, Congress mandated that this research activity among others be carried out by the Department. We understand that, subsequently, the Office of the Secretary coordinated the assignment of responsibilities and tasks required to fully implement the legislative research program. Now it appears unclear whether the National Institute of Health or the Health Care Financing Administration (HCFA) is primarily responsible for financing and administering the continuation of dialyzer research beyond Phase I.

The Office of Inspector General has become involved with the objective of finding a solution to this situation. Unless HCFA and NIH can arrange to work together and resolve this issue, we plan to notify the Congress.

Therefore, we would appreciate your immediate and full cooperation in responding to this letter. We request that a formal, written explanation which outlines your position on this issue be returned to this office no later than close of business January 27, 1981.

Addressees:
Dr. Nancy Cummings, Director, Institute of
Arthritis, Metabolism and Digestive Diseases
National Institute of Health
James M. Kaple, PhD., Director, Office of
Research, Demonstrations and Statistics
Health Care Financing Administration

cc:
Martin Strosberg, ASPE
Tom Antone, OS Ex. Sec.
Vic Zafra, FDA
Seymour Perry, PHS

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFAR
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Acting Assistant Inspector General,
Health Care and Systems Review, DHHS

DATE: January 28, 1981

FROM : Associate Director, NIAMDD/NIH
Kidney, Urologic and Blood
Diseases Program

SUBJECT: Telephone Conversation (1/28/81) about Dialyzer Reuse memo which was never received

P.L. 95-292 contained the "End Stage Kidney Disease" (ESRD) amendments to the Social Security Act. These included a passage recommending studies to reduce the cost of ESRD treatment and charged the Secretary, HEW, to conduct several studies including a study of reuse of dialyzers. No funds were made available for dialyzer reuse studies, nor was responsibility assigned formally to any PHS Agency. The Artificial Kidney Chronic Uremia Progam (a contract program), NIAMDD, NIH, issued an RFP for such a study of dialyzer reuse. When this contract program was absorbed into the Kidney, Urologic and Blood Diseases Program, NIAMDD, in mid-Fall 1979, because no funds were available and because these studies were not deemed to be scientific research, the decision was made to limit an award to a one-year pilot study by contract.

The information enclosed is about dialyzer reuse that was prepared in response to an inquiry by the Secretary, HEW, after receiving the Inspector General's Service Delivery Assessment. The major portion of the enclosure is Chapter XII from the Technical Report, "Investigation of the Risks and Hazards Associated with Hemodialysis Devices", prepared for the FDA Bureau of Medical Devices in 1980.

When Dr. James M. Kaple, Acting Director, Office of Research, Demonstrations and Statistics, HFCA, received his copy of your memo he called me to discuss this issue. We concur that since the issue about dialyzer reuse is one of SAFETY of dialyzer reuse, it would appear to belong more appropriately within FDA's sphere of responsibilities.

Excuse the apparent tardiness of this response. After the initial telephone conversation with Elizabeth Kelley (1/14/81), Health Care and Systems Review, we never received a written memo.

Nancy Boucot Cummings, M.D.

Enclosures

REUSE OF HEMODIALYZERS

The practice of cleaning and sterilizing "disposable" hemodialyzers to use for another dialysis for the same patient (dialyzer reuse) has aroused controversy recently. In the early dialysis era, reuse generally was common and accepted because of the shortage of equipment, supplies, personnel, and money to pay for this expensive treatment. Since the passage of Amendment 20I, PL 92-603 and the consequent payment for the majority of dialysis costs by the Federal government, there was a marked increase in availability of supplies, as well as fiscal relief for ESRD patients.

The Health Industry Manufacturers Association has declared its opposition to dialyzer reuse in a publication, "Multiple Use of Single-Use Hemodialyzers" (1). The National Association of Patients on Dialysis and Transplantation (NAPDT) has taken a stand opposing reuse except in controlled experiments (2). The Food and Drug Administration issued a policy statement, January 27, 1977, on reuse of disposable devices which places the responsibility for safety and effectiveness of reused devices on the physician (3). The Veterans Administration banned reuse of disposable devices, but granted an exception after the economic impact of dialyzer reuse was better understood (4).

Numerous reports in the literature attest to the fact that dialyzer reuse can be safe and effective. Dr. Blagg reported on 255 patient years of experience with home reuse without serious problems reported to his senior staff (5).

When the process is not carefully controlled, medical problems associated with reuse have occurred, which frequently are associated with high residual sterilant. When formaldehyde is used to sterilize new or used dialyzers, anti-N-like antibodies may be detected in patients exposed to such dialyzers (6).

First use of new dialyzers is not free of medical complications. Dr. Odgen, University of Arizona, described "new-dialyzer syndrome": respiratory distress, back and chest pains, chills and/or fever which have an onset within a few minutes of starting dialysis. He postulates that this syndrome may be due to plasticizers, particulates, sterilant residuals (or reaction products), residual bore fluid, pyrogens or bacteria (7). Earlier, Ogden et al demonstrated adverse reactions due to formaldehyde residuals and residual 2-chloroethanol present in new dialyzers (8).

Other points of significance are:

- The specific procedure used for restoring a dialyzer is the most important determinant in final outcome - a recommendation in "Investigation of the Risks and Hazards Associated with Hemodialysis Devices," an FDA Medical Devices Standards Publication, which presents an extensive balanced discussion about dialyzer reuse assembled by Dr. Keshavian et al (13).

- Dialyzer reuse is widespread.
- Seventeen percent of the dialysis facilities in the United States employed multiple usage of dialyzers, and treated approximately 16% of patients, Renal Physicians Association, 1978, (9).
- Dialyzer reuse is practiced by 18.5% of facilities in 26 European countries. The highest rate is in the United Kingdom, where an estimated 56% of patients practice reuse (10).
- No significant difference in mortality of dialysis patients in the hospital or home dialysis setting with or without reuse (A. Wing, 1977-78 Survey, UK) (11).
- The nephrology community must develop its own standards for reuse as a medical standard: one conclusion of the International Conference of Multiple Usage of Dialyzers, 1979, (12).

Additional data from carefully controlled studies is necessary to resolve the remaining issues associated with reuse. The National Institute of Arthritis, Metabolism, and Digestive Diseases currently supports a careful laboratory evaluation of reuse procedures. Following the successful conclusion of this study, additional carefully controlled clinical trials should be undertaken. Plans for these trials are under discussion with the Health Care Financing Administration and with the Food and Drug Administration.

National Institute of Arthritis, Metabolism
and Digestive Diseases
Associate Director, Kidney, Urologic and
Blood Diseases Program
9/22/80

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2. National Association of Patients on Dialysis and Transplantation: Dialyzer reuse - NAPHT's statement of position, May 1979.

3. Food and Drug Administration, Bureau of Compliance, Policy Statement - January 27, 1977: Reuse of disposable devices.

4. Veterans Administration: Circular 10-78-214, September 12, 1978; and, Circular 10-79-200, August 28, 1979.

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6. Nolph, K.D., Husted, F.C., Sharp, G.C.: Antibodies to nuclear antigens in patients undergoing long-term hemodialysis. Am J. Med 60: 673-86, 1976.

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11. Wing, A.: Experience and cumulative outcome data on multiple usage of dialyzers from the EDTA registry and studies in the United Kingdom. International Conference on Multiple Usage of Dialyzers, National Nephrology Association, New York, N.Y., *in press*.

12. Deane, N.: Summary. International Conference on Multiple Usage of Dialyzers, National Nephrology Foundation, New York, N.Y., *in press*.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date 2/81

From Acting Director
Office of Research,
Demonstrations and Statistics

Subject Response to Your Request for Information Pertaining to Kidney Dialyzer Reuse

To Ronald D. Schwartz
Acting Assistant Inspector General
for Health Care and Systems Review

This is in response to your January 15 memorandum concerning responsibility for financing and administering research with respect to kidney dialyzer reuse. I believe a brief chronology of events occurring subsequent to the passage of P.L. 95-292 would be helpful in clarifying our position on this issue.

BACKGROUND

P.L. 95-292 mandated that "The Secretary...conduct a study on the medical appropriateness and safety of cleaning and reusing dialysis filters by home dialysis patients. In such cases in which the Secretary determines that such home cleaning and reuse of filters is a medically sound procedure, the Secretary shall conduct experiments to evaluate such home cleaning and reuse as a method of reducing the costs of the...program." The Senate Findnce Committee Report accompanying P.L. 95-292 indicates that "experiments in the reuse of dialysis filters would be conducted only after the Secretary of HEW has determined following review by appropriate authorities such as the FDA, the Center for Disease Control or the National Institutes of of Health, that the study will be carried out under circumstances that will assure that the filter reuse will be safe and medically appropriate." (Underlining added for emphasis.)

After P.L. 95-292 was enacted, the Department divided responsibility for the studies and experiments mandated by the legislation between HCFA and PHS. PHS agreed to assume lead responsibility for the medical appropriateness of dialyzer reuse (see Attachment 1, Memorandum from Julius Richmond to Robert Derzon, dated October 20, 1978). In that memorandum, PHS indicated that they expected to be reimbursed by HCFA for all research pertaining to their responsibilities under the legislation. HCFA responded to PHS (see Attachment 2, Memorandum from Leonard Schaeffer to Julius Richmond) that we expected PHS "to arrange for obtaining funds to conduct studies of...the medical appropriateness of dialyzer reuse." PHS did not respond to this memorandum; subsequently, however, PHS did initiate limited studies on the reuse of dialysis filters. PHS' plans with respect to dialyzer reuse were stated in the Secretary's Report to Congress on ESRD studies and experiments (see Attachment 3). As the report indicates on page 4, PHS did plan on conducting a clinical evaluation of re-used dialyzers as a final phase of a project in FY 1981 (which is consistent with PHS' overall responsibility for determining medical appropriateness).

The industry has expressed a tentative interest in being involved in clinical trials and it is possible that their support could offset some of the PHS expenses. HCFA is willing to continue reimbursement for costs associated with filter reuse for Medicare beneficiaries until PHS completes their studies.

HCFA's responsibility under the dialyzer reuse study is to determine the cost impact of dialyzer reuse, but these studies can not be initiated until PHS certifies that reuse was safe and medically appropriate. HCFA is prepared to undertake such studies, as soon as PHS certifies to the medical appropriateness of filter reuse for home dialysis patients.

Department Actions to Date

HCFA and the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) have made strides pursuing this issue. The NIAMDD is now completing a preliminary in vitro study of dialyzer reuse which includes an assessment of alternative dialyzer reprocessing and testing procedures. This study, which was to be completed in early January, has been extended by NIAMDD for 90 days. Concurrently, HCFA's Office of Special Programs is conducting its own literature review and discussions with interested parties, i.e., NIAMDD, the Food and Drug Administration (FDA), dialyzer manufacturers and their interest groups, and leading nephrologists.

Phase I NIAMDD study, for example, may be sufficient for setting dialyzer reprocessing standards without clinical trials. The practice of reuse has been widely established with no conclusively documented adverse effects. Uniform standards, if approved by the medical community, would perhaps suffice. Further, the recent development of an automated dialyzer cleaning device, the Lixivitron (not yet FDA approved), may make reuse acceptable without further research. Finally, industry may introduce reusable dialyzers or the cost of single use devices may decrease to the point where the issue becomes moot prior to the completion of any research.

#FK-1

APR 2 1981

Acting Director
Bureau of Medical Devices

Dialyzer Reuse Research

Ronald D. Schwartz
Acting Assistant Inspector General
for Health Care and Systems Review

This is in response to your February 25, 1981 memorandum concerning responsibility for financing and administering research with respect to kidney dialyzer reuse.

We have reviewed the documentation attached to your memorandum, particularly the National Institutes of Health (NIH) and the Health Care Financing Administration (HCFA) responses. We disagree with Dr. Cummings' (NIH) statement that the responsibility for conducting dialyzer reuse research "...would appear to belong more appropriately within FDA's sphere of responsibilities." Moreover, we found no evidence of concurrence with such statement in Mr. Keple's (HCFA) memorandum of January 28, 1981.

The FDA position on the reuse of single-use disposable dialyzers is described in a January 5, 1981, memorandum from the Commissioner of Food and Drugs to the Assistant Secretary for Health (copy attached). The memorandum states: "When an institution or practitioner chooses to reuse a single-use hemodialyzer, the responsibility for the safety and effectiveness of the reused device shifts from the manufacturer to the party responsible for the reuse."

A well-designed clinical study addressing the overall safety of reuse versus single-use might be desirable, however, such a study is not within the mission of the FDA. Such research should be performed by agencies equipped and staffed for research activities.

The FDA is responsible for regulating the manufacturing of any medical device that may be used for dialyzer reprocessing and for dialyzers labeled for reuse. The FDA is not aware of any conventional dialyzer labeled for reuse that is in commercial distribution. Consequently, unless a manufacturer can demonstrate otherwise, dialyzers intended for reuse would be classified into Class III. This means that such dialyzers would be subject to premarket approval unless a manufacturer successfully submits a petition for reclassification.

Either route of FDA review would require extensive data in support of dialyzer reuse, including specific procedures for dialyzer reprocessing. The burden of such investigations would be with the manufacturer.

As mentioned in Mr. Kaple's (HCFA) memorandum on January 28, 1981, an automatic computerized dialyzer reprocessing device called the Lixivitron, has been developed. The manufacturer of Lixivitron is United Medical Products, Inc. At the American Society of Nephrology (ASN) meeting of November, 1980, the company displayed their device and announced that they have submitted a premarket "notification" to the FDA for a determination of substantial equivalence. This "notification" is still under review by the FDA.

I hope this information explains our position and our responsibilities under the law. Please contact me if we can assist you further.

/s/ Victor Zafra
Victor Zafra

Enclosure

cc:
HFK-1 R/F
HFK-400
HFK-420
HFK-100
HFK-115
HFK-300 R/F
HFK-310
HFA-224 Records
LKOBREN:mlc:3/25/81
Revised: 3/26/81/LKOBREN:mlc
Revised: 3/30/81/LKOBREN:mlc
Revised: 4/01/81:LKOBREN:mlc
HF-1

APR 9 1981

/S/

Edward L. Kelly, Acting Director
Office of Special Programs, HCFA

Multiple Use of Dialyzers

Nancy Cummings, M.D., Director
Kidney, Urologic and Blood Diseases, PHS

The purpose of this memorandum is to follow up on our previous discussions regarding the multiple use of dialyzers. In your most recent letter, you state that "while a considerable number of reports of research results have appeared on the topic of multiple use, the sum of the studies is not considered adequate for the basis of a government policy decision."

We believe that a medical practice which has been employed in this country and parts of Europe for nearly 20 years with few documented complications cannot be considered experimental. Recent data indicate that more than 16 percent of facilities are now practicing reuse and many of these are large freestanding facilities. In view of these facts, we believe there is sufficient evidence to make a decision that reuse is a generally safe, efficacious, and cost effective procedure, when appropriate standards are met for reprocessing the dialyzers.

The single most important issue, in our minds, is the development and promulgation of standards including criteria for patient selection. These standards could parallel the format of facility standards currently existing (see attached). With the forthcoming publication of a rule on incentive reimbursement for dialysis facilities, we believe that reuse will proliferate. In the absence of medically acceptable standards, this could lead to significant decreases in the quality of dialysis provided to end-stage renal disease beneficiaries. However, if Federal standards existed, the survey and certification process could be used to monitor the use of such guidelines, thereby assuring quality care for patients.

We believe that such standards would be most effective if they were consensus standards, developed by all interested parties, including physicians, manufacturers, and all involved government agencies - the National Institutes of Health, the Center for Disease Control, the Food and Drug Administration, and the Health Care Financing Administration. Therefore, we recommend that you call a meeting upon the receipt of Dr. Deane's study to pursue the development of reprocessing standards. It is suggested that this meeting be scheduled for May or June so that policy action can be implemented prior to publication of a final incentive reimbursement rule. We would be happy to assist in the preparations for such a conference in any way we can; however, we believe it would be more appropriate if conducted under the auspices of the National Institutes of Health.

Attachment

Prepared by:HSQ/OSP/ORSMD/DIESE:XXXXXXXXXPBURDETTE:ark 73086 4/7/81

Volume Testing and Storing the Hollow Fiber Kidney for Reuse

A. Turn machine "Off".

B. Remove Hose #6 from #6 on kidney and attach to white connector.

C. Holding basin under #5 on kidney, remove Hose #5 from #5 on kidney. Put basin on floor to catch any fluid dripping from #5 on kidney.

D. Connect Hose #5 to other end of white connector.

E. If you do not intend to reuse your kidney, go on to "Rinsing and Sterilizing Machine" and "Storing Blood Tubing".

F. If you do intend to reuse your kidney, go on to Step #1.

SUPPLIES NEEDED

1" White tape and marking pen
Measuring pitcher
2 quick disconnects
2 clamps (hemostats)
Timer
2 pieces short thin latex tubing
4 pinch clamps

1. Make sure water is turned on at the tap and DI tank.

2. Clamp Line #1 and remove from #1 on kidney.

3. Attach a small thin piece latex tubing to End #1 of kidney.

4. Attach D3 (Drain Line*) to latex tubing on #1 of kidney.

   * First time at home you must make your own D-3 by taking a long segment of large latex tubing and label it D-3. Place one end in drain. Put a 5 in 1 connector on the other end.

5. Rotate Kidney to #2 end up. Clamp Line #2, then remove Line #2 from #2 kidney end.

6. Attach a small thin piece of latex tubing to end #2 of kidney.

7. Attach R4 (filtered water) to latex tubing on #2 end of kidney. Rotate kidney to #1 end up.

8. Make sure all clamps on tubing are removed and then turn filtered water (R4) on ______ turns.**

   ** IMPORTANT----Do Steps A thru D below for the first time at home.

   a. Place drain line (D-3) in large basin.

   b. Turn filtered water on 2 turns.

   c. Measure outflow into measuring pitcher for 10 seconds (use your stop watch).

   d. The correct amount is 200-300 cc in that 10 second period (adjust filtered water knob accordingly).

9. Set timer for 20 minutes.

   A. With fingers, pinch and release R4 tubing several times to force

27. Pump 1/2 liter of formaldehyde through kidney while pumping:
    a. With fingers, pinch and release tubing on #2 kidney end to force air up to #1 end.
    b. Tap on #1 end to remove all air.
28. When 1/2 liter has gone through, clamp latex tubing on #1 end using a pinch clamp.
29. Clamp latex tubing on #2 kidney end using a pinch clamp.
30. Clamp F2 on formaldehyde jug and disconnect from latex tubing on #2 end.
31. Remove D3 (drain line) from latex tubing on #1 end of kidney. (Hold D3 up in the air to drain any fluid in line back into drain).
32. Put quick disconnects on #5 and #6 of kidney.
33. Attach F2 on formaldehyde jug to quick disconnect on #5 kidney end.
34. Hold a basin under quick disconnect on #6 kidney end.
35. Remove clamp on F2 on formaldehyde jug.
36. Pump formaldehyde through until fluid comes out of quick disconnect on #6, then clamp quick disconnect with pinch clamp.
37. Clamp quick disconnect on #5 with pinch clamp.
38. Clamp F2 on formaldehyde jug.
39. Disconnect F2 from #5.
40. Disconnect air pump from F1 on formaldehyde jug and reattach F1 to F2.
41. Using a piece of white tape, label kidney with "Formaldehyde", "Date", and K-2 or K-3, etc. (This means kidney has been used that number of times).
42. Rotate Kidney to #1 end "down".

Proceed with "Storing Blood Tubing".

Revised: August, 1980

Rinsing the Parallel Plate Kidney for Reuse

1. Leave Kidney with #1 end "Up".
2. Fistula Patients - Check that:
    - a. Blood pump tubing is removed from blood pump and Line #4 from line clamp.
    - b. Monitor line is removed from blue drip bulb.
    - c. Photocell is removed from "Open" hole and place into "Blind" hole.
3. Remove Hose #6 from #6 on kidney and attach to white connector.
4. Holding basin under #5 on kidney, remove Hose #5 from #5 on kidney. Put basin on floor to catch any fluid dripping from #5 on kidney.
5. Connect Hose #5 to other end of white connector.

    NOTE: IF YOU ARE GOING TO STORE BLOOD TUBING ONLY, PROCEED WITH PROCEDURE "STORING BLOOD TUBING."

6. Make sure water is "On" at tap.
7. Using a short thin piece of latex tubing, attach Line #4 to R4. (R4 is the filtered water outlet.)
8. Using a short piece of latex tubing, attach Line #3 to D3* (Drain).

    * First time at home you must make your own D-3 by taking a long segment of large latex tubing and label it D-3. Place one end in drain. Put 5 in 1 connector into other end.

9. Remove all clamps and turn filtered water "On" ____ turns.** (Your instructor will mark this.)

    ** IMPORTANT----before you do this at home for the first time do the following steps:

    - a. Place drain line (D-3) into large basin.
    - 10" b. Turn filtered water on 2 1/2 turns.
    - c. Measure outflow into measuring pitcher for 10 seconds (use your stop watch).
    - d. The correct amount is 200-300 cc in that 10 second period (adjust filtered water knob accordingly).
10. Now proceed with "Rinsing and Sterilizing the Machine".

Remainder of Parallel Plate Kidney Sterilizing

1. Turn filtered water "off" at R4.

2. Clamp Line #4.

   Gather supplies: Diluted Formaldehyde 1.5% (8 liter jug)
   Air pump
   Measuring pitcher
   1 gallon bleach (any brand)
   2 clamps
   2 quick disconnects
   2 pinch clamps
   Alcowipes
   1 bleach bottle

3. Put 40 cc. bleach into empty measuring pitcher.

4. Pour bleach into bleach bottle.

5. Add 1000 ML. hot tap water to bottle and put cap on bleach bottle.

6. Remove Line #4 from R4. Leave latex tubing on R4.

7. Attach Line #4 to B4 on bleach bottle. Clamp latex tubing on B4.

8. Hang bottle on I.V. pole. (Do not elevate.) Remove old saline line and bag from I.V. pole and set aside.

9. Attach air pump to B1 on bleach bottle.

10. Set a timer for 5 minutes. Proceed with Step 11.

11. Remove all clamps on blood tubing and bleach bottle and pump bleach through kidney. KEEP READING.

12. When bleach in bottle is down to 800 ML. clamp Line at #3.

13. Keep pumping your air pump until black needle on air pump gauge stays at 300.

14. Then clamp Line at #4.

15. Clamp B4 on bleach bottle.

16. During the 5 minutes, squeeze drip bulbs with a clamp to remove any stubborn clots or fibrin.

17. Disconnect air pump from B1. Disconnect Line #4 from B4 on bleach bottle.

18. Attach Line #4 to R4 (on filtered water outlet). When timer rings, go to Step 19.

Remainder of Parallel Plate Kidney Sterilizing

1. Turn filtered water "off" at R4.
2. Clamp Line #4.

   Gather supplies:
   - Diluted Formaldehyde 1.5% (8 liter jug)
   - Air pump
   - Measuring pitcher
   - 1 gallon bleach (any brand)
   - 2 clamps
   - 2 quick disconnects
   - 2 pinch clamps
   - Alcowipes
   - 1 bleach bottle

3. Put 40 cc. bleach into empty measuring pitcher.
4. Pour bleach into bleach bottle.
5. Add 1000 ML. hot tap water to bottle and put cap on bleach bottle.
6. Remove Line #4 from R4. Leave latex tubing on R4.
7. Attach Line #4 to B4 on bleach bottle. Clamp latex tubing on B4.
8. Hang bottle on I.V. pole. (Do not elevate.) Remove old saline line and bag from I.V. pole and set aside.
9. Attach air pump to B1 on bleach bottle.
10. Set a timer for 5 minutes. Proceed with Step 11.
11. Remove all clamps on blood tubing and bleach bottle and pump bleach through kidney. KEEP READING.
12. When bleach in bottle is down to 800 ML. clamp Line at #3.
13. Keep pumping your air pump until black needle on air pump gauge stays at 300.
14. Then clamp Line at #4.
15. Clamp B4 on bleach bottle.
16. During the 5 minutes, squeeze drip bulbs with a clamp to remove any stubborn clots or fibrin.
17. Disconnect air pump from B1. Disconnect Line #4 from B4 on bleach bottle.
18. Attach Line #4 to R4 (on filtered water outlet). When timer rings, go to Step 19.

Remainder of Parallel Plate Kidney Sterilizing
Page 2

19. Remove clamp from Line #3, then Line #4.
20. Turn filtered water "on" at R4 to preset mark.
21. A. Set timer for 5 minutes.
    B. Remove bleach bottle from I.V. pole and discard remaining bleach.
22. When timer rings, pull back 5 cc. water into heparin syringe.
23. Turn filtered water "off" at R4.
24. Clamp Line #4.
25. On Formaldehyde jug (diluted--large 8 liter container; disconnect F2 from F1 (leave white connector in F2).
26. Remove Line #4 from R4. Leave latex tubing on Line #4.
27. Attach Line #4 to F2 on Formaldehyde jug.
28. Attach air pump to F1 on top of Formaldehyde jug.
29. Place clamp on Line #3.
30. Remove clamp from F2 and Line #4.
31. Pressurize air pump to 200. When you reach 200 on air pump, remove clamp from Line #3 and pump through 1/2 liter of formaldehyde.
32. When 1/2 liter has gone through, clamp Line #3 (by drain).
33. Disconnect heparin syringe from heparin line. Push out any fluid into a basin and reattach heparin syringe to heparin line.
34. Pull back 5 cc. Formaldehyde into heparin syringe.
35. Clamp Line at #4 and also clamp F2.
36. Leaving latex tubing on Line #4, disconnect Line #4 from F2.
37. Disconnect Line #3 from D3. (Leave latex tubing on D3).
38. Connect Line #3 and #4 together using short thin piece of latex tubing on Line #4.
39. Remove all clamps from blood tubing.
40. Put quick disconnects on #5 and #6 of kidney.

41. Attach F2 to quick disconnect on #5 of kidney.

42. Hold empty basin under quick disconnect on #6 of kidney and have pinch clamp ready.

43. Remove clamp from F2 on Formaldehyde jug and pump formaldehyde through kidney.

44. When fluid comes out of quick disconnect at #6 on kidney, clamp quick disconnect using the pinch clamp.

45. Clamp quick disconnect on #5 of kidney using another pinch clamp. Clamp F2. Disconnect F2 from #5 of kidney.

46. Disconnect air pump from F1. Reattach F2 to F1 (leave clamp on F2).

47. Rotate kidney so #5 end is "up".

48. Using a piece of 1" white paper tape, label kidney with "date" and "K-2, T-2", or "K-3, T-3", etc. (which means kidney and tubing have been used that number of times.)

49. Using marking pen, label heparin syringe "Formaldehyde".

50. Wipe outside of blood tubing with alcohol to remove any dried blood.

51. Turn water "off" at tap and DI tank. Turn power switch "ON" and let water pressure drop to "O". Turn power switch "OFF".

52. Proceed with "Storing Saline Line" procedure.

April 15, 1981

Westwood Building, Room 621
AC 301-496-7571

Comments on the ESRD Program Evaluation Plan

Dr. Seymour Perry
Director, National Center for Health
Care Technology
Parklawn Building, Room 17A29
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Perry:

Overall, I believe it is commendable that the agency and authors have assembled an evaluation plan covering the complex set of issues associated with the end stage renal disease program. Having the multitude of issues and questions discussed in one comprehensive document is very helpful. On the whole the document makes a very positive contribution.

The first group of comments which follow are addressed to the document as a whole, and the second set of comments will concern specific sections.

In the discussion on Monday, April 13, it was evident that an addition to the plan, such as an appendix, which describes the current status of on-going research or evaluation projects in a summary form would be most helpful. Such an addition would also provide for each project the names of the persons responsible, date the evaluation started, the expected completion date, and how to get reports. Much of the information which was given verbally at the meeting on Monday had to do with current activities. To the lone reader of the plan, such information would be valuable in order to understand the overall effort.

My view is that it does not seem very helpful to include in the evaluation plan, copies of all the data forms being used by the medical information system. It is unnecessary detail that one would go into as a separate issue if one wished to evaluate the data being sought by the medical information system.

In the Monday discussion, I received the impression that the entire plan would be pursued in a more or less equal way depending on particular future needs or interests and availability of funding. In my view it would be more helpful to have a formal priority assessment for the entire plan, which should be done in as open and as realistic a manner as possible. As everyone recognizes, this is an era of limited resources. As an example of the need for priority setting, it would be very helpful to have data on the relative cost of patients maintained through transplantation and dialysis, as well as medical outcomes, overall relative rehabilitation, etc. The relative costs of each major mode of therapy for ESRD should be known, prior to launching any serious major effort to increase transplantation, unless it is clearly superior medically or economically. Thus it would follow that high priority

Some comments on details are listed in the following section:

On page 4, there is a discussion of the difference between the dialysis rate in the United States compared to Europe. The question is raised as to whether this is a difference in health policy or a difference in epidemiology of the disease. The study of this issue, for example, is an area where it is exceedingly important to get excellent medical and epidemiological input into the methodology to be used, before such a study is launched.

In the discussion of application of transplantation to pediatric patients, compared to dialysis, the lack of growth and sexual maturation of the pediatric dialysis patient is not mentioned.

On the same page, the statement is made that unlike dialysis, the number of transplants being performed has not significantly increased since 1972, when in fact, it has increased approximately 33%.

As additional discussion of background to the plan, it would be helpful to include an overall discussion of the environment of the ESRD program including other government agencies which interface with ESRD, the nephrology community, and other organizations of both scientists, and physicians, the networks, the patient organizations, the nurses and social worker organizations, etc.

In Chapter 3, Page 5, CAPD is discussed as another dialysis modality, and the statement is made that the cost of CAPD is less than either home or facility dialysis. There is no high quality data available on the cost of CAPD. Taking into consideration hospitalization costs, it may be that the cost of CAPD is more than the cost of home hemodialysis and may equal or exceed the cost of in-center hemodialysis. Now, the facts are not known.

In further description of the study of modality choice on page 7, it is stated that the analysis would include such measures as health status of the patient. Presumably this would be whether the patient had other disease complications in addition to chronic renal failure. Again, in this instance it would be most essential to have expert medical assistance in the design of data forms, as well as physician input into evaluation of pilot study data to be certain that the data being gathered are reasonably reliable.

In the discussion of modality choices, Chapter 3, study area Number 1, page 16, survival analyses are described. The inability to distinguish between home and facility dialysed patients and between live and cadaveric donor transplanted patients is noted. It would obviously be necessary to correct these deficiencies if reasonable comparative survival data are to be generated. It is well known that the dialysis population represents an older group with more concomitant diseases, than are the patients selected for transplantation.

In the discussion of the dietary studies of study area Number 4, on page 37, under resource requirements the comment is made that the NIH trial on dietary control needs to be replicated. The NIH trial (which has been completed) was a study of the feasibility of patient compliance with a low protein diet. It was a precursor to the type of study which is required now. The study now required which is discussed to some degree in the previous pages, does indicate that there would be a comparison of the patients (utilizing the low protein diet for a period of time) compared to those patients who are placed upon dialysis at an earlier point in their therapy. The NIH study was confined to the question of whether patients with low renal function (but who could survive without dialysis), could in fact, be persuaded to observe the low protein diet in reasonable numbers. Thus the study described is one which utilises information developed in the previous NIH study, but makes a more advanced, critical comparison.

In the discussion of area 4, dialyser reuse, on page 38, in the background there are some statements which are incorrect. Reprocessed dialysers, do not necessarily require greater pressures for removal of fluid from a patient than a new dialyser. Even in the event that greater pressure is required, this would have little influence on patient discomfort. Also in the background statement, the cost of the new dialysers is probably understated. In the discussion of methods and measures to be used, mention is made of developing indicators of patient acceptance at home and facility, but no statement is made about physician acceptance. Physician acceptance is the key element in determining any modifications of the therapy of the ESRD patient, and should be a prime factor in the study design. If additional clinical trials are conducted, a number of medical outcomes need to be measured. Certain of the comparative measurements to make between patients maintained exclusively on new dialysers compared to patients maintained on reprocessed dialysers according to specific reprocessing technique are frequency of adverse symptoms during therapy, and longer term, any differences in immunological response. In the further discussion of resource requirements under the same topic, mention is made of using essentially the same study design as the current NIH study replicated at 3 or 4 centers. The NIH study has been confined to being a laboratory feasibility study to demonstrate that a reprocessed dialyser has performance characteristics which are essentially in the same range as a new dialyser. The NIH study did not undertake a longer term examination of any clinical factors including adverse patient responses during therapy nor any measures of immunological response. In the NIH study, the attempt was made to show that performance characteristics of reprocessed dialysers, residual sterilant content, and sterility status are in reasonable ranges to use reprocessing techniques.

In the discussion of study area 7, impact of new technology, on page 48, the statement is made that another potentially beneficial area is the use of kinetic modeling of laboratory tests to channel some patients into a less frequent dialysis schedule. The term kinetic modeling is appropriate but should be used in terms of describing the weekly dialysis prescription to maintain certain individuals rather than stating it in terms of laboratory tests. The point is, that certain patients with some residual renal function can be maintained with kinetic modeling on a less frequent dialysis schedule. The question which remains to be answered, however, is whether the greater fluctuations in blood chemistries would produce an adverse response relative to the more conventional three times a week therapy There are no current, modern data available to assess this issue. Older data on dialysis frequency studies usually had too many other covariables to be used for a valid judgement on this question.

The above comments are meant to be constructive and helpful. I would be glad to answer any questions or discuss any of these or other issues in more detail if it is desirable.

Sincerely,

Robert J. Wineman, Ph.D.
Program Director
Chronic Renal Disease Program
National Institute of Arthritis, Diabetes
and Digestive and Kidney Diseases

cc: Dr. Cummings

Arthur D Little Inc.

ACORN PARK
CAMBRIDGE MASSACHUSETTS 02140
(617) 864-5770

JOHN M KETTERINGHAM
VICE PRESIDENT

April 23, 1981

Norman Deane, M.D.
National Nephrology Foundation
40 East 30th Street
New York, NY 10016

Dear Norman:

I tried to call you to discuss the status of the final report to NIAMDKD on the reuse study. I talked to Dr. Wineman who tells me that you have prepared a further draft which is presently being reviewed and modified.

As we agreed, I would appreciate the opportunity to review and contribute to the final version before it is published, particularly if our report to you is referred to in any form other than the entire document. I think you might find this constructive and helpful. Perhaps we could consider a meeting with Dr. Wineman to discuss the report sometime in the near future.

With kind regards.

Very truly yours,

John M. Ketteringham

s
cc: Dr. Robert Wineman
Dr. Mildred Broome
Alyce M. Wood

[illegible]

Manhattan Kidney Center

40 East 30th Street, New York, New York 10016

Norman Deane, M.D.
Medical Director

May 4, 1981

John M. Ketteringham, Ph.D.
Arthur D. Little Inc.
Acorn Park
Cambridge, Mass. 02140

Dear John:

We are working on the final report of the NIAMDD Contract.

Your letter suggests a misunderstanding since I did not agree at any time to give you review prerogatives on the final report. Where your subcontractor's report is referred to, it will be in context and with proper attribution.

I think it would be interesting for us to meet with Dr. Wineman and discuss the report if at all possible. I should mention that I have not been authorized expenditure of funds to ADL from the Foundation since the inception date of the Contract. Consequently, if ADL staff participates in any meeting with NNF staff, the Foundation cannot provide any of the expenses which may be involved.

With kindest regards.

Very Truly Yours,

Norman

Norman Deane, M.D.

ND:jmcd

cc: Robert J. Wineman, Ph.D.
Mildred Broome, Ph.D.
Alyce M. Wood

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date May 6, 1981

From Nancy Boucot Cummings, M.D. NBC
Associate Director, KUBD/NIADDK

Subject Multiple Use of Dialyzers

To Edward L. Kelly, Acting Director
Office of Special Programs, HCFA

In response to your memo which we received April 20, 1981, I would like to note our support in principle of the utility of planning a meeting to discuss dialyzer reuse. However, there are two facets to the issue which you raise about development of reprocessing standards. The most important one, which could be a very controversial and volatile one, is that dialyzer reprocessing is considered by us and by practicing nephrologists to be a component of medical practice. It would be advisable that suggested guidelines be developed by a non-governmental, "neutral" group such as the one which worked on guidelines for water purification. Second, it is inappropriate for the NIH to sponsor a meeting for standards development since this does not fall within our responsibilities. I have discussed your request with G. Donald Whedon, NIADDK Director who notes "to hold and conduct a meeting on standards of practice is clearly not NIH business." He continues, it would be acceptable for me as a representative of NIH to attend as "an interested and knowledgeable party."

We would be more than glad to assist you in your planning of a conference should you feel it must be done. Both Dr. Wineman and I believe it would be preferrable to have such a meeting sponsored by a non-governmental group. An appropriate group which might be willing to accept such a responsibility for development of guidelines for dialyzer reprocessing is the ASAIO-AAMI Renal Disease and Detoxification Committee of which Dr. Ronald Easterling is chairman. There is precedent for their interest in dealing with such issues evidenced by their involvement with evaluation of quality of dialysate water. After such a group has reported their findings and possible recommendations, HCFA and other agencies could consider how they wish to respond to such recommendations. The expertise available to such a group would be similar to that which would be acceptable to the field and probably that which we would suggest. The acceptance by the nephrology community would be obtained more readily if this route were followed. We cannot emphasize too strongly the importance of the government not dictating a mode of practice.

There are a few practical issues to consider. Dr. Deane's final report is not completed. Probably it would take about 6 months to organize an initial conference on development of guidelines in draft form. Additional time would be necessary for comments, revisions, and further consideration. The next meeting of Dr. Easterling's committee is in Anaheim at the ASAIO meetings, 1:00 p.m., Friday, May 8.

Do let us know if we can be of further assistance. We continue to have a strong scientific interest in dialyzer reuse, albeit, it is inappropriate for us to work on regulations.

MAY 21 1981

Director, Division of Gastroenterology-Urology and General Use Devices
Bureau of Medical Devices (HFK-420)

Reuse of Hemodialyzers

Stuart L. Nightingale, M.D.
Acting Associate Commissioner for Health Affairs (HFY-1)
Through: Acting Director, Bureau of Medical Devices (HFK-1) /s/ 5-26-81
Associate Director for Device Evaluation,
Bureau of Medical Devices (HFK-400) /s/ 5/22

At the April 13 meeting of the Gastroenterology-Urology Panel Section, the Panel strongly and unanimously recommended to the Food and Drug Administration to request a Consensus Development Conference on the reuse of hemodialyzers. The Panel members felt that such a conference would be the proper forum to discuss and define the present state-of-the-art of hemodialyzer reuse. Reuse is a controversial practice used in a significant portion of the end-stage renal disease (ESRD) patient population in the United States and abroad. The Panel members were aware of Congressional interest in hemodialyzer reuse, and that the only Government effort toward resolving this issue is being terminated this year (see attachment).

Issues to be addressed during the conference might be the following:

a) scientific issues related to hemodialyzer reuse;

b) safety of hemodialyzer reuse;

c) hemodialyzer reprocessing procedures;

d) socio-economic aspects of hemodialyzer reuse;

e) statistics on hemodialyzer reuse in the U.S. and abroad; and

f) recommendations.

Since reuse of hemodialyzers is an issue of significant importance for the Government, physicians, and patients, I endorse the Panel recommendation and request that this issue be brought up to the Technology Coordinating Committee for further consideration.

Fernando Villarroel, Ph.D.

bcc: HFA-224
HFK-1 YZafra
HFK-400 RSKennedy
Attachment
HFK-420 FVillarroel-File
HFK-420 FV Chron
[illegible]/FVillarroel/dls/5/20/81

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDES

GUIDE 7124.16

CHAPTER 24 - DEVICES

SUBJECT: Reuse of Medical Disposable Devices

BACKGROUND:

Investigations by the Food and Drug Administration (FDA) and other Federal agencies have disclosed that a number of health care institutions have engaged in the practice of reusing single use sterile disposable medical devices. Such devices may not be amenable to resterilization and/or reuse. The FDA is not aware of any data which would establish conditions for the safe and effective cleaning and subsequent resterilization and/or reuse of any disposable medical devices.

In January of 1975, the Bureau of Health Insurance of the Social Security Administration issued State Agency Letter No. 29 concerning the Reuse of Disposable Guidewires and Catheters. The letter stated that such devices were not to be reused. Since that time, the FDA has received a number of inquiries relative to the economics of its policy as related to issues concerning protection of the public health, and has been requested to reconsider and reevaluate the position it has taken.

The FDA, in recognition of the validity of the concerns expressed by all parties involved in this matter has reviewed it's position on this issue, but finds that there is a lack of data to support the general reuse of disposable medical devices, including disposable guidewires and catheters. The fact that devices are labeled disposable is indicative of this lack of data. In order for a device to be considered "reusable", it must be capable of withstanding necessary cleaning, and resterilization techniques and methods, and continue to be safe and reliable for its intended use.

The FDA has concluded, therefore, that the institution or practitioner who reuses a disposable medical device should be able to demonstrate: (1) that the device can be adequately cleaned and sterilized, (2) that the physical characteristics or quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use. Moreover, since disposable devices are not intended by the manufacturer or distributor for reuse, any institution or practitioner who resterilizes and/or reuses a disposable medical device must bear full responsibility for its safety and effectiveness.

POLICY:

The reuse of disposable devices represents a practice which could affect both the safety and effectiveness of the device. Information developed regarding this practice should be referred to the Bureau of Medical Devices for review and evaluation.

JULY 31, 1981

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date Edward Kelly

From Edward L. Kelly, Acting Director
Office of Special Programs, HCFA

Subject Hemodialyzer Reuse

To Carolyne K. Davis, Ph.D.
Administrator
Health Care Financing Administration

THRU: Regina McPhillips

Per your recent request, information on the potential savings, incidence and safety issues of hemodialyzer reuse is presented below. I have also included a summary of recent developments in this area.

POTENTIAL SAVINGS

The literature on the topic of dialyzer reuse contains numerous estimates of the potential savings attributable to the practice. These estimates, which range from $100 to $200 million per annum, vary considerably in their base assumptions. These assumptions, which include the number of reuses, the concurrent reuse of blood tubing, the cost per dialyzer, and the cost per reuse, all impact significantly upon ones estimate of savings.

If reuse, as currently practiced, was extended to 100 percent of facilities with no changes in the surrounding environment, the potential savings could be as high as $150 to $200 million. However, it is likely that facilities inexperienced in reuse will, at least initially, assume a more cautious approach, and it is expected that manufacturers will increase prices to recapture a percentage of their losses. Consequently, we have chosen a conservative approach for our savings computation.

When discussing savings, an additional caution should be added. Under current reimbursement regulations, hospital-based facilities are reimbursed for cost while freestanding facilities are reimbursed on a charge basis. Consequently, savings to hospitals due to reuse could be recaptured by the Federal Government, but there is no assurance that there would be any Federal savings for the approximately 45 percent of patients treated in freestanding facilities. Further, any attempt to require facilities to pass these savings on could result in a significant decrease in reuse. However, it is quite possible that the bulk of these savings would accrue to the Government under the proposed incentive reimbursement system if no rate adjustments are made for dialyzer reuse. Therefore, it is important to consider the impact of our reimbursement system on the distribution of savings.

It is estimated that expansion of dialyzer reuse to 100 percent of facilities in 1980 would have yielded a savings of approximately $87 million. Our computation is presented below:

o Assumptions

1)	Cost of new dialyzer	$22.50
2)	Cost of reprocessing	$ 7.50
3)	Number of reuses per dialyzer	5
4)	Number of dialysis sessions per patient/per year	156
5)	Number of potential[1] reuse patients	44,512

o Computation

- Cost per patient/per year:

With Reuse		Without Reuse	
26 new dialyzers @ $22.50	= $ 585	156 new dialyzers @ $22.50	= $351
+ 130 reuses @$7.50	= $ 975		
Total Cost	= $1560	Total Cost	= $351

- Net savings:

Savings per patient year	$ 1950
X Number of potential patients	44,512
Total Savings per year	$86,798,400

If the annual increase in the end-stage renal disease (ESRD) patient population remains constant at 15 percent, the savings projections, with no inflation adjustments, would be $100 million and $115 million for calendar years 1981 and 1982, respectively.

INCIDENCE OF REUSE

In a recent Centers for Disease Control (CDC) survey, 18 percent of over 1000 respondents reported that they reuse dialyzers in their facility.[2] In a 1978 study, the Renal Physicians Association reported that the reuse population represented 16 percent of hemodialysis patients. Hence, it is estimated that in 1980, approximately 8,100 patients in 180 facilities were treated with reused dialyzers. The incidence of reuse is expected to increase considerably. National Medicare Care (NMC) which now owns 30 percent of

[1] Excludes positive Hepatitis B and peritoneal dialysis patients. Based upon 1980 hemodialysis population.

[2] Facilities which practice reuse exclusively with home patients were excluded. Approximately 10 percent of the surveyed facilities did not respond

freestanding facilities is instituting the practice in all of its facilities. Further, recent Food and Drug Administration approval of an automated dialyzer reprocessing device will make dialyzer reuse more attractive and available to the dialysis community.

SAFETY ISSUES

Numerous risks to patient safety have been attributed both to reuse and first use of hemodialyzers. These issues are outlined below:

REUSE ISSUES

1) Infection Risk - It has been argued that there is a risk of hepatitis exposure to both patients and staff due to either cross-use of dialyzers or exposure to blood by reprocessing technicians. The Centers for Disease Control has recently issued a report which refutes this argument. The CDC study showed no association between increased hepatitis B risk and reuse.

2) Formaldehyde Induced Antibodies - There have been reports of antibody formation in dialysis patients attributed to blood-formaldehyde reactions in reused dialyzers. These antibodies (anti-N-like ~~antibodies) have been alleged to contribute to immunological~~ changes which can result in increased risks of transplant rejection. There is, however, no scientific data to support the connection between these antibodies and transplant rejection at this time. Existing research does support the absence of antibody formation when formaldehyde concentration is kept within acceptable standards.

3) Pyrogenic Reactions - There have been reports of fever and chills related to hemodialysis treatment in general, and reuse, in particular. Researchers have clearly linked these phenomena to dialysis facility water systems. Improvements in water treatment systems have minimized this problem. It should be noted that CDC has recently identified increased levels of endotoxins associated with new dialyzers, apparently introduced in the manufacturing process.

4) Decreased Dialyzer Performance - It has been reported that patients treated with reprocessed dialyzers may be underdialyzed. While this can cetainly be true if no minimal performance criteria are employed, most facilities which reuse report no meaningful reduction in dialysis clearances within the specifications they have set. In regard to another performance issue, it should be noted that the incidence of blood leaks is considerably higher with new dialyzers.

FIRST USE ISSUES

1) Neutropenic Response - There have been reports of transient reductions in white blood count following the first use of a dialyzer. This response is considerably reduced on subsequent uses. It should be noted that this phenomenum has not been linked to deleterious effects to patient health.

2) First Use Syndrome - The medical literature has reported incidences of adverse physical patient reactions occurring only on first use of a dialyzer. These reactions have largely been in the form of pyrogenic type, and chest and back pain. This problem has been minimized when new dialyzers are reprocessed prior to their first use.

While more controlled, scientific studies of these safety issues are needed. It is clear, at this point, that there is little documented evidence of a safety risk associated with dialyzer reuse. As stated in our decision memo of May 28, the principal factor impacting on the safety of reuse relates to the standards employed for reprocessing the dialyzers.

RECENT DEVELOPMENTS

Since our memo of May 28, there have been several new developments which impact on the reuse issue. First, the National Institutes of Health has released a final report on a laboratory study of dialyzer reuse. This report, the most comprehensive study of the topic to date, provides considerable scientific data in support of reuse. Further, an evaluation of reprocessing techniques, which could form a basis for the development of standards, is presented. Second, in response to the concerns of the Health Care Financing Administration (HCFA) and the Food and Drug Administration (FDA), a conference was held at the National Center for Health Care Technology (NCHCT) on July 17 to discuss concerns within the Department on this issue. It was concluded that a major workshop should be held in October or November to develop and release a Departmental position on dialyzer reuse, initiate development of reprocessing standards, and identify any further actions required. Initial planning calls for broad representation in the conference with participants to include representatives of Federal, industry and patient interests.

Funding of this conference, however, may present a problem. While NCHCT expressed a willingness to pay for it, their continued existence for FY 1982 is now under Congressional consideration. Therefore, it is quite possible that HCFA may be called upon to provide monies in support of this conference.

This summarizes the information you recently requested as well as recent developments related to dialyzer reuse. If you require any additional details, please let me know.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
HEALTH CARE FINANCING ADMINISTRATION WASHINGTON, D.C. 20201

OFFICE OF THE ADMINISTRATOR

August 11, 1981

Note to Drs. Rubin and Brandt:

The attached background memo related to dialyzer reuse is but one of a number of initiatives I believe we need to take in order to contain the costs of ESRD.

Another initiative is to encourage more kidney transplantations.

I would like to discuss these ideas and others at one of our forthcoming trio meetings.

Carolyne K. Davis

Attachment

BUREAU OF MEDICAL
DEVICES
Z-158a
AUG 21 1981

DIRECTOR'S
OFFICE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date October 7, 1981

From Contracting Officer, NIADDK

Subject Telephone Conversation Re: National Nephrology Foundation Contract

To William Ketterer
HHS General Counsel
Building 31, Room 2B50

This is a follow-up to our telephone conversation yesterday.

The question was posed as to whether a final report submitted by a subcontractor to a contractor under the terms of the subcontract could be disclosed upon request to a third party, or simply made public by the Government in the same manner as the Contractor's final report to the Government under the terms of the contract would be disclosed or made public. Your answer to me was no; that since the subcontract final report was submitted to the contractor, the Government did not have possession of the subcontract report. Therefore the Government could not disclose or make public what it did not possess.

It is requested that you confirm this information by endorsement of this memorandum, and returning it; or by separate memorandum to me.

Harvard Gregory
Harvard Gregory

CONCUR: William [illegible] 10-15-81

PUBLIC HEALTH DIV.
...E of GENERAL COUNSEL
RECEIVED

OCT 9 1981

Arthur D Little, Inc [illegible]

October 9, 1981

Norman Deane, M.D.
National Nephrology Foundation, Inc.
40 East 30th Street
New York, NY 10016

Dear Dr. Deane: Re: Contract No. NO1-AM-9-2214

As you know, the final report on the subject contract, "Multiple Use of Hemo dialyzers," dated June 1981, was prepared by the Manhattan Kidney Center printed and submitted to the NIAMKDD without benefit of review at Arthur Little, Inc. (ADL). The report contained data and text taken from our repor to the National Nephrology Foundation, Inc., (NNF), "The In-Vitro Evaluation Certain Issues Related to the Multiple Use of Hemodialyzers," dated Februar 1981, prepared under subcontract. While reference was made to the subcontrac report, the material selected has been edited, supplemented and interpreted b you, your staff and others.

In these circumstances, we suggested it would be helpful for us to review th final report. Dr. Wineman asked that we summarize any substantive comment in a letter. We have confined ourselves to issues relating to our work, an particularly to any conclusions which appear to be based on our data. Clearly however, the interpretations and conclusions presented in the final report t NIAMKDD are those of the National Nephrology Foundation and not of Arth D. Little, Inc.

In general, we believe the report fails to make clear where material reference to ADL's and other authors' work begins and ends. Also, we urge that conclu sions which could be applied to clinical practice, such as those relating to th concentration of formaldehyde used for sterilization, be substantiated wher appropriate by clinical trials, as was envisaged in the original request fo proposal for this assignment.

The final report omits most of the limitations which attended data and statis tical statements in the ADL report, for those ADL-generated data and state ments which were selected. In particular, the final report tacitly asserts tha the dialyzers which NNF submitted to ADL for testing were sufficient in numbe and representation to permit conclusive statistical comparisons. The ADL repor makes no such assertion, and in fact advises in several places that "mor extensive testing be performed to substantiate" its qualified findings.

There are a number of tables presenting data or statistical conclusions in the NNF report which are attributed to the ADL report when in fact the tables, either in total or in part, are not derived from the ADL report. These are addressed in the comments which follow.

Since our report to the NNF is a major reference, we hope that it, this letter, and the attached comments will be made readily available to those receiving copies of the final report.

Very truly yours,

John M. Ketteringham
Vice President

Attachment (1) 4 pages

cc: Dr. Robert J. Wineman
National Institutes of Health

Sylvan Nathan, Esq.
Nathan & Nathan

COMMENTS ON "MULTIPLE USE OF HEMODIALYZERS"

Page	Paragraph	Comment
4	1	The data in the report (see Figures 5, 6A, 6B, 7A, 7B, 8 and 9) shows that clearance values steadily fall as cell volume is reduced. This relationship is analyzed. It is not accurate to say that, "functional aspects of the dialyzers are maintained until there is a reduction of cell volume of approximately 60%."
	2	The predictive precision of the relationship is not given.
6	2	We believe that any change in clinical sterilization practice must be supported by adequate clinical studies.
8	2,3	We believe that clinical studies are required to substantiate this conclusion.
42	Table 8	ADL did not calculate the means reported in this table, as ascribed.
43	Table 9	ADL did not perform the statistical comparisons S vs. N and C vs. N described in this table, as ascribed. Moreover, the means for C (urea; simple), C (inulin; simple) and C (inulin; complex) do not coincide with those in the ADL report.
45	Table 1	The data for dialyzer "4" presented in the ADL report, p. 40, has been omitted. While this dialyzer showed a reduction of cell volume to 62 ml after only one use, measurements of clearance were consistent with this value.
46	Table 11	ADL did not perform the statistical comparisons in this table, as ascribed.
47	Table 12	ADL did not calculate the means reported in this table, as ascribed.
48	Table 13	ADL did not perform the statistical comparisons of ultra filtration reported in this table, as ascribed.

COMMENTS ON "MULTIPLE USE OF HEMODIALYZERS" (Continued)

Page	Paragraph	Comment
49	3,4	Since problems with mass balance closure have been endemic to studies of this kind , it would be helpful to have more complete data presented. Also, was the apparatus exactly the same as used at ADL and described in Appendices 7 and 8?
51	1	Data omitted from Table 1, page 45, indicates that "dialyzer function" is not always maintained after single use.
	2,3	See comment on p. 4.
53-62		Since this analysis uses data from ADL, a more direct reference would seem appropriate.
72	Table 16	ADL did not perform the statistical comparisons in this table, as ascribed.
73	Table 17	ADL did not perform the statistical comparisons in this table, as ascribed.
102	1	Incubation of antimicrobials with test organisms was done in test tubes not in Petri dishes.
107	3	The pour plate method can be used reliably after 10-fold or more dilution of 0.2% formaldehyde or with no dilution of samples containing 0.2% glutaraldehyde, 0.8% Betadine or 0.02% peracitic acid (See Table on p. 218 of Appendix 10).
108	2	Formaldehyde at 0.05% produced a 6-log kill of Pseudonomas aeruginosa after 5 and 24 hours; however, 0.1% formaldehyde was required to obtain a 6-log kill of Escherichia coli after 5 and 24 hours. Note that the data point at 5 hours for 0.05% formaldehyde in panel A of Figure 33 was plotted incorrectly when this figure was transcribed from ADL Report Figure 17, page 76. The 5 hour CFU/ml was about 1.8×10^5, not 1×10^0.
108	Table 27	Missing data points in this table can be obtained from Figures 30-33, i.e.: Formaldehyde vs. E. coli, 0.1% Formaldehyde vs. Staph aureus, 0.2% Glutaraldehyde vs. C. albicans 0.2% Betadine vs. E. coli 0.2%, not 0.8%.

---

* C. Colton - private communication

COMMENTS ON "MULTIPLE USE OF HEMODIALYZERS" (Continued)

Page	Paragraph	Comment
109	Table 28	Incomplete set of data. See Table 21, page 85 of ADL report.
110	Figure 30	Vertical axes should read CFU/ml not cells/ml. The smallest number on the vertical axes which are a log scale should read 1×10^0 not 0.
111	Figure 31	Same as Figure 30.
112	Figure 32	Same as Figure 30.
113	Figure 33	Same as Figure 30. Also note in Panel A show data point for 5 hour 0.05% formaldehyde is 1.8×10^5 not 1×10^0.
114	Table 29	Table 29 (studies not conducted at ADL) is presented before it is discussed in Section 2 at the bottom of the page and could be mistakenly attributed to ADL.
118	1	Table 28 should read Table 30.
120	2	The results discussed were obtained in in vitro experiments. Exposure of test organisms was done in test tubes not in Petri dishes; assay for survivors was done in Petri dishes.
121	1	We believe clinical trials are needed to confirm the in vitro test results of sterilant concentrations.
122	2	The apparent discrepancy of potency of Betadine noted by Favero et al. (Ref 68, which is a personal communication to Dr. Deane) might also be explained if Favero's experiments had been conducted in the absence of protein. Note that the ADL in vitro studies were done in the presence of a protein load (Appendix 10, page 214).
122	3	Although this does not refer to work performed at ADL, note that 0.2μ filters are referred to as 0.22 "mcg" filters. No data are presented to support the statement that "A comparison of results obtained by the pour plate method and the membrane filter technique, however, did not demonstrate consistently higher counts when the pour plate method was again used with P. aeruginosa taken directly from an agar slant."

COMMENTS ON "MULTIPLE USE OF HEMODIALYZERS" (Continued)

Page	Paragraph	Comment
124	3	Table 28 should read "Table 30."
125	2	Note the para "5" is para "4" — no data is presented.
126	1	Data with artificially inoculated dialyzers in the ADL report which are not incorporated in the NNF report address this point. See pages 86-99 of the ADL report, especially the last paragraph of the discussion on page 99. These conclude that the experimental sterilization procedure (involving 0.2% formaldehyde) might fail to attain a six-log Staph aureau "flush and kill" for certain used Travenol 1200 dialyzers.

November 18, 1981

Building 31, 9A17
AC (301) 496-9091

Mr. Michael J. Miller
Executive Director
Association for the Advancement
  of Medical Instrumentation
Suite 602
1901 N. Ft. Myer Drive
Arlington, Virginia 22209

Dear Mr. Miller:

Thank you for your letter concerning the need for an alternate plan to hold a conference on Reuse of Hemodialyzers. While our staff fully agrees that such a conference is needed, we have been cooperating with Dr. John Sadler in his effort to arrange for a conference to be held in Washington March 1-2, under sponsorship of a coalition of societies. As we understand it, active sponsorship is possible from the American Kidney Fund, The National Kidney Foundation, The American Association of Nephrology Nurses and Technicians, The National Association of Patients on Hemodialysis and Transplantation, and The American Society of Artifical Internal Organs. In the recent planning meeting our understanding was that Dr. Sadler would also be seeking the cooperation of your society to participate in the joint sponsorship of the conference. It may also be possible for Dr. Sadler to arrange for some support from interested federal government agencies.

Our view is that a Conference on Reuse is most appropriately handled by a coalition of interested societies from the private sector. Our staff will lend its cooperation to this effort. Our hope would be that AAMI will also contribute its effort and support.

If you have any additional questions concerning the roles of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, or the participation of the Institute's staff, please let me know.

Sincerely,

Nancy B. Cumm

Nancy B. Cummings, M.D.
Associate Director
Kidney, Urologic, and Hematologic Diseases
National Institute of Arthritis, Diabetes,
  and Digestive and Kidney Diseases

cc: Dr. Sadler
bcc: Dr. Wineman, NIADDK ✓
Dr. Villarroel, FDA ✓
Mr. Plonsky, HCFA
Dr. Favero, CDC, Phoenix

Association
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AAMI

November 6, 1981

Nancy B. Cummings, M.D.
Associate Director
Kidney, Urologic & Blood Diseases Program
National Institute of Arthritis, Metabolic
and Digestive and Kidney Diseases
National Institutes of Health
Building 31, Room 9A17
Bethesda MD 20205

Dear Doctor Cummings:

The Association for the Advancement of Medical Instrumentation is concerned that the cancellation of the planned NCHCT Conference on Reuse of Hemodialyzers will delay the development of consensus recommendations on this very important issue. Because we feel that recommendations on hemodialyzer reuse are urgently needed, we offer our assistance, in cooperation with relevant federal agencies, in making this conference a reality.

As you know, in addition to our Proposed American National Standard for Hemodialysis Systems, the AAMI Renal Disease and Detoxification Committee is currently drafting a similar standard for hemodialyzers. Perhaps the most critical issue facing this committee is that of hemodialyzer reuse. Committee members had been awaiting the results of the planned NCHCT conference to provide them with the consensus recommendations needed to guide them in their deliberations.

In addition, a recent survey of California dialysis centers, conducted to assess the need for a short course on bacteriology and water treatment during our 1982 annual meeting in San Francisco, revealed an almost universal interest in and request for information on hemodialyzer reuse.

Because of the critical need for establishment of consensus recommendations on this issue, and because AAMI has an establihsed mechanism for conference and guideline development, we would like your endorsement for an AAMI sponsored conference on reuse of hemodialyzers.

Although the cost of planning, developing and executing the conference would be largely borne by AAMI, we are also interested to know if funds are available from your agency to assist in this regard. AAMI sponsorship of the conference is not contingent upon outside funding, however. We would hope that your agency would, in any event, consider cosponsoring the conference by designating a representative to participate in the conference, thus helping to assure that all viewpoints are represented.

Nancy B. Cummings, M.D.
Page 2
November 6, 1981

I look forward to hearing from you soon relative to this inquiry. Should you have any questions about this proposal, please don't hesitate to contact Phyllis Freedman, or myself.

Sincerely yours,

Michael J. Miller
Executive Director

cc: Robert Wineman, Ph.D.
Ronald E. Easterling, M.D.
Kenneth D. Serkes, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date February 18, 1982

From James F. Donovan, M.D.
Chairman, ESRD Strategic Work Group

Subject Chairman's Report—INFORMATION

To Secretary
THRU: Administrator, HCFA:____
US:____
ES:____

At the initiation of the Administrator, Health Care Financing Administration, and with your support at the recent Operations Management System presentation by the Administrator, a Departmental End Stage Renal Disease Work Group was established to address the multiple issues involved in the End Stage Renal Disease Program. This is a multi-faceted Program with many controversial issues and was addressed by the Departmental Work Group during the months of October 1981 through January 1982. The product of their efforts is the attached report (Tab A).

Tab B lists the membership of the Departmental Work Group. In addition to the members of this group, I met with various outside organizations and groups who have interest in the End Stage Renal Disease Program. Tab C lists the organizations or groups with whose representatives I met and solicited their input.

In order to obtain a concise and cohesive response to various issues, each member of the Departmental Work Group and the representatives of the special interest groups were asked to provide position papers on the issues of concern to them. Volume I, which accompanies this report, represents a synopsis of the Departmental papers with preliminary cost estimates where available and annotated bibliography of all papers submitted. Tab D is a table of contents for this volume.

Volume II, also accompanying this report, contains all the original papers, both Departmental and private sector. Tab E contains a table of contents for this volume, indicating which documents were submitted by the private sector groups.

In an attempt to allow you to set priorities, allocate resources, and make decisions, the various issues identified were prioritized by the Work Group, and the four highest priority options are presented for your decision. This priority ranking was based on a vote by the Departmental Work Group and represents their consensus of the most pressing issues in the End Stage Renal Disease Program. These proposed decisions are not mutually exclusive. Each proposal and its accompanying decision will require additional resource commitment or reallocation of existing resources.

We have attempted to format each issue in a consistent manner; and where possible, cost estimates have been included with each issue so that you have a more clear picture of the cost/benefits related to each particular area of the End Stage Renal Disease Program.

The issue of rate setting for dialysis payment has not been addressed as a specific issue, as we felt it was inappropriate for this group to address an issue which is presently under consideration for rulemaking. Many subjects (i.e., CAPD complications, nutritional therapy, etc.) have not been presented as options for your consideration at this time, as the Work Group felt that the highest priority issues should be presented to you first. However, all the issues which could be identified within this Program were addressed and the results are in Volumes I and II. From this information, options for other specific issues could be developed for your consideration in order to proceed with the formulation of a comprehensive ESRD strategy.

I hope this document is of assistance to you in developing priorities and allocating resources for the End Stage Renal Disease Program. I would be happy to discuss them with you and present to you the many aspects of this program which we have identified in our attempt to provide you with a global and comprehensive view of this program.

Attachments
Tab A--ESRD Report
Tab B--Membership of Interdepartmental ESRD Work Group
Tab C--Special Interest Representatives Interviewed
Tab D--Table of Contents for Volume I
Tab E--Table of Contents for Volume II

REPORT

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ATTACHMENT A

Introduction

This paper develops information/options concerning the improved management, efficiency and cost effectiveness of the End-Stage Renal Disease (ESRD) program. Discussion on alternative Medicare reimbursement methods has been excluded considering the currently pending regulations on incentive rate reimbursement. Additionally, the Office of the Assistant Secretary for Health Research, Statistics and Technology requested that an initiative covering a multi-faceted assessment of the state-of-the-art of health care delivery for the ESRD population be included. However, this proposal was received too late to be systematically reviewed by the task force and, as a result, has not been included with this submission.

The initiatives developed include areas, e.g., improvement of the Departmental data base, where results can be realized in the short term (1-3 years), and other areas, e.g., prevention of diseases leading to ESRD, where identifiable results will take longer to realize.

Two approaches were used in developing these options. First, HCFA convened a Department-wide work group to prepare option and background papers focusing on:

1. ESRD Program Data Strategy
2. Prevention
3. Biomedical Research
4. Program Research and Evaluation
5. Transplantation
6. Dialyzer Reuse
7. Treatment Modalities/Options
8. Rehabilitation
9. Prospective Payment
10. Eligibility Determinants

Secondly, to assure that the concerns of Congress and of ESRD interest groups were addressed, issue papers discussing various aspects of many of these areas were solicited from the private sector and testimony from the recent ESRD hearings before the Senate Finance Committee was considered. The workgroup reviewed these materials and compiled the final options package. Not all of the materials submitted or all of the testimony has been included in the body of the options package. However, the background materials have been included in:

Volume I: synopses of Department papers including preliminary cost estimates, where available, and an annotated bibliography of all papers submitted;
Volume II: originals of all Department and private sector papers and related testimony.

The ESRD program management information/options outlined in this memorandum can be summarized as follows:

Data:

- A description of HCFA's current activities in the development of ESRD data to support program management.
- A proposal to improve the Department's ESRD data base in order to provide a sound foundation for policy development, research initiatives, program management, decision making, and resource allocation.

Prevention:

— A brief discussion of the potential means of preventing diseases causing ESRD.

— A three-part proposal to: 1) initiate a primary prevention program focused on the education and behavior modification of the hypertensive and toxic nephropathy population; 2) encourage research into the basic process of the diseases responsible for ESRD so that means to prevent these diseases or their progression to ESRD may be developed; 3) encourage basic and clinical research into the physiological processes which occur in renal disease in order to enhance the possibility of early detection of preventable conditions which lead to ESRD.

Research and Evaluation:

— A description of the current biomedical research agenda of the National Institutes of Health and of the Health Care Financing Administration's current and proposed program research and evaluation plan.

— A proposal to undertake further analysis to develop a cohesive clinical and program research plan directed to the goals of reducing the incidence of ESRD, of improving the treatment of ESRD and of developing program steps to improve the economy and efficiency of ESRD care.

Transplantation, Reuse and Rehabilitation:

— Background covering the current issues in kidney transplantation and in hemodialyzer reuse.

- Proposals to improve: the information base on transplantation; immunology therapy, and kidney harvesting and preservation techniques; and public education covering donor consent.
- A proposal to undertake a major clinical trial to determine effects of hemodialyzer reuse.
- A review of the current HCFA-sponsored study of the impact of alternative types of therapy on quality of life, quality of care, cost of care and rehabilitation potentials of ESRD patients; and of the mission of HCFA's Rehabilitation Task Force. Since proposals concerning rehabilitation options will result from these activities, none are being presented here.

Each of these options addresses an area of Departmental activity that is critical o the achievement of improved ESRD program management and the delivery f efficient, cost effective health care. In considering these areas we have attempted o develop the initiatives which have the greatest "pay off" potential.

Background

n 1972 Congress passed PL 92-603 which first authorized funding for the End-tage Renal Disease program. In the enacting statute, as well as in subsequent egislation (PL 95-292, 1978), Congress articulated the mission of the ESRD program: o assure patient access to high quality, cost effective medical care. The ESRD rogram, in keeping with Congressional intent, has established the following goals nd objectives in carrying out its mission:

- To ensure that beneficiaries who have been diagnosed as having ESRD receive the care they need;
- To encourage proper distribution and effective utilization of ESRD treatment resources while maintaining or improving the quality of care;
- To provide for the efficient delivery of appropriate care by physicians and facilities; and
- To encourage self-dialysis or transplantation for the maximum practical number of patients who are medically, socially and psychologically suitable candidates for such treatment.

In the time since the initial legislation, the ESRD program has been the subject of increased attention by policy-makers and legislators largely because of the magnitude of program expenditures, 1.6 billion dollars for over 70,000 beneficiaries in 1981. In addition, the ESRD program touches upon extremely sensitive political, medical, scientific, technological, social, ethical, economic and programmatic issues.

The largest single factor influencing the increase in program cost is the increasing number of Medicare beneficiaries receiving care. The following tables have been included to demonstrate this. The tables show: 1) distribution of per capita Medicare reimbursements for all services to ESRD beneficiaries by type of service; 2) the total number of Medicare enrolled ESRD beneficiaries by age, by year; and 3) a comparison of total Medicare reimbursements, the ESRD population and per capita reimbursement by year. Actual reported data are shown for calendar years 1974-1979; estimates are included for 1980 and 1981.

Section 4: Transplantation, Reuse and Rehabilitation

Transplantation:

Proposal: To develop a research plan to improve the results of kidney transplantation, to develop a prototype public education format to encourage organ donation and to reestablish a transplant information data base.

Background

During 1980, 4,697 transplants were performed in 149 facilities across the country. This constituted an increase of 12.1 percent over 1979. Of the total number of transplants in 1980, 72.9 percent (3,422) were from cadaveric donors and 27.1 percent (1,275) from living donors.

Most studies indicate that transplantation of kidneys from living donors produces the highest degree of success while cadaveric kidneys are reported to be significantly less successful. The American Society of Transplant Surgeons, in a recent study, reported a failure rate of 20-25 percent in living donor transplants at 2 years as opposed to a 30-43 percent failure rate for cadaveric donors at 2 years. In general, the literature shows a wide range of success for both living and cadaveric donor transplantation.

Much of this variance may be attributed to factors such as: transplant surgical team; number of transplants performed per year by facility; HLA/DR antigen matching; haplo-typing; unique patient characteristics. Despite the fact that each transplant unit tracks this information for their own patients and that many transplant hospital centers maintain their own registries, definitive national data are not currently available.

Secondly, for the last decade, the Uniform Anatomical Gift Act has governed organ donation in the United States. Under the provisions of this Act, consent must be obtained on a voluntary basis from any individual 18 or older to donate at the time of death all or specific organs for transplantation or other purposes. The Act also provides that relatives of the deceased may also act to donate organ provided that the decedent's expressed wishes are not violated.

The prime donors are people in generally good health between the ages of 5 and 60. Optimal conditions are required to harvest kidneys. The surgical removal (nephrectomy) should occur in operating rooms where appropriate equipment for kidney preservation is available. Transplantation should occur within an avera time of 24-48 hours (range: a few hours to 5 days) after removal of the kidney from the cadaver. It is more difficult to utilize kidneys from potential donors who die of cardiac arrest. Donors with a malignancy (except central nervo system malignancies), kidney infections, systemic diseases affecting the kidney, and history of prolonged high blood pressure are precluded from kidney donation.

Most hospitals with renal transplant certification maintain their own registry of kidney patients. At the national level, coordination among these hospitals regarding cadaveric donors is primarily achieved by the United Network for Organ Sharing. However, despite this coordination system, of a total of 4,260 cadaveric kidneys harvested, only 3,422 or 80% were transplanted in 1980. The Organ Sharing Subcommittee of the American Society of Transplant Surgeons recently submitted a proposal to NIH to establish a centralized national kidney transplant data program to coordinate information about patients awaiting renal transplants and available harvested kidneys. This proposal was received late, thus it was not able to be systematically reviewed by the task force.

Finally, public opinion about the importance of organ donation for kidney patients nd medical research has generally not kept pace with developments in transplantations. ocal effort of various hospitals, and regional transplantation and organ donor rganizations have influenced public opinion, but generally only in localized areas. Consequently, successful donor consent registration efforts have not produced he maximum results desired. Efforts by national voluntary health organizations uch as the National Kidney Foundation have done much to focus public attention n this issue; and they should be encouraged to expand their efforts. However, e need to determine what efforts the Department could undertake directly indirectly in coordination with the private sector that would produce a substantial crease in the volume of organ donations.

Initiatives:

For the Department, together with the American Society of Transplant Surgeons and other renal organizations, to reestablish a national transplant registry. This registry would provide information on kidneys harvested, patient type and matchin characteristics and other relevant information on kidney donors and patients. (The information gathered in this registry would be post-transplant. Transplanted patients would be followed for a minimum of 36 months post-transplant).

To undertake a study to examine current surgical removal techniques; existing methods for kidney preservation, such as kidney perfusion machines; current mechanisms and systems for either donor kidney or recipient transportation; transplantation surgery techniques and immuno-suppressive therapy. Also, it is recommended that this study determine as well what factors contributed to the wastage of over 800 kidneys in 1980.

For the Department to consider ways in which public and professional information on kidney donation can be enhanced. It is recommended that this effort be coordir with other organ donation efforts to maximize not only availability of kidney donors but all other donors as well.

Dialyzer Reuse:

Proposal: To undertake a prospective clinical trial to determine the efficiency and safety of reuse and to identify potential long-term effects of prolonged reuse.

Background:

The dialyzer membrane, whether hollow fiber, coil or plate, is an indispensable component of hemodialysis. The dialyzer provides filtration through which the blood is cleansed of any impurities which exist as a result of kidney disfunction. Dialyzers, though labeled disposable and not specifically recommended by FDA for reuse, have been reused in the United States since the mid-sixties, a practice which is even more widespread today. According to a 1979 Renal Physicians Association survey, some 17 percent of the total dialysis population were engaged in the reuse of disposable hemodialyzers; and with the advent of a new medical devise for cleaning and disinfecting, this number will undoubtedly increase.

At present, there have been no formal clinical trials performed in the United States to determine the clinical safety and efficiency of hemodialyzer reuse. However, there are some preliminary indications that such reuse may not pose a danger to hemodialysis patients.

o CDC, in a comparative study of their hepatitis B survey of 1976 and the Renal Physicians Association's 1979 survey, concluded that reuse of hemodialyzers did not appear associated with increased risk of hepatitis

- While there is a lack of data to support general reuse, FDA has indicated that for a device to be considered reusable it must be capable of being adequately cleaned and sterilized. Further, the physical properties or the qualitative integrity of the device must not be adversely affected and it must continue to be safe and reliable.

- An NIH/NIADDK-supported contract found that the utilization of specified sterlization and disinfecting procedures with suitable process and quality control can produce a reprocessed hemodialyzer equivalent to a new one.

- Both the National Kidney Foundation and the National Association of Patients on Hemodialysis and Transplantation have indicated that hemodialyzer reuse can be accomplished safely.

- In contrast, opposition to widespread hemodialyzer reuse comes from the Health Industry Manufacturing Association which opposes such a practice.

Initiatives:

To authorize the Director of FDA to undertake a prospective clinical trial employing discrete hemodialyzer sterilizing and disinfecting procedures. The study would report its findings from which generalizations could be drawn not only regarding efficiency and safety but the long-term effects of prolonged reuse of demodialyzers. The final report would include a specific set of recommendations for standards that could be incorporated into regulatory authority to govern hemodialyzer reuse.

bcc: M. Broome
R. T. Murphy
A. Sivak
A. Wood

Arthur D Little, Inc. ACORN PARK · CAMBRIDGE MA 02140 · (617) 864-5770 · TELEX 921436

March 15, 1982

Dr. Robert J. Wineman
National Institutes of Health
Westwood Building, Room 621
Bethesda, MD 20205

Dear Bob:

I read in the MDDI Report, "Gray Sheet," of March 8, 1982, page 3, that, "an amended version" of the report, "Multiple Use of Hemodialyzers," was released at a "Dialyzer Re-Use Workshop," on March 1, 1982.

As you know, this report contains substantial pieces of work conducted at Arthur D. Little, Inc., and we would appreciate receiving a copy. Does this version address the various comments and corrections made by Arthur D. Little, Inc., to you in our letter of October 9, 1981? Or is our letter to be made available to those persons receiving this report?

I note that the "Gray Sheet" records that 2% formaldehyde is "recommended" by this report. Our opinion is that the scientific data contained in the original version of the report did not support a recommendation, but merely showed that in specific in vitro conditions, 2% formaldehyde achieved a high kill of certain representative pathogens. We recommend further data be generated before any recommendation is made regarding clinical practice.

Sincerely,

John

John M. Ketteringham
Vice President

s
cc: Norman Deane, M.D.

CAMBRIDGE MASSACHUSETTS
[illegible] LONDON MADRID [illegible] SAN FRANCISCO SÃO PAULO TOKYO TORONTO WASHINGTON WIESBADEN

March 19, 1982

Westwood Building. Room 621
AC (301) 496-7571

Dr. John M. Ketteringham
Vice President
Arthur D. Little, Inc.
Acorn Park
Cambridge, MA 02140

Dear John:

In response to your letter of March 15th, a copy of the amended report "Multiple Use of Hemodialyzers" is enclosed. The revision was prepared by Dr. Deane taking into consideration the comments and corrections noted in your letter of October 9th to Dr. Dean. We have no plans to distribute the letter of Arthur D. Little, Inc. with the report.

For your information the revised report is now available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161.

The PB number is PB 82 .166349. The price is $21.00 for a paper copy and $4.00 for microfiche.

Sincerely,

Robert J. Wineman, Ph.D.
Program Director
Chronic Renal Disease Program
National Institute of Arthritis, Diabetes,
and Digestive and Kidney Diseases

Enclosure

July 29, 1982

D.H.H.S. Public Health Services
Food and Drug Administration
Room 900, U.S. Custom House
2nd and Chestnut Streets
Philadelphia, PA 19106

To Whom It May Concern:

I am requesting, under the Freedom of Information Act (F.O.I.), the following information in reference to medical devices used by a Physician contrary to the label. Item, artificial kidney disposable dialyzer, which is F.D.A. labeled ONE TIME USE ONLY. I request in writing your policy on the reuse of this item as I am a patient of 12 years and my unit is considering the reuse of this single use item.

Thank you for your attention on this most important matter.

Sincerely,
Robert Rosen
Robert Rosen

Address: 6332 Powder Horn Ct.
Bensalem, PA 19020

Phone # 752-5718

F82-20533

RECEIVED
AUG 5 1982
FDA FOI STAFF (HFI-35)

LI #2308

Rec'd.
7/30/82

September 20, 1982

Mr. Reynolds
Food and Drug Administration
Freedom of Information
8757 Georgia Avenue
Silver Spring MD 20910

Dear Mr. Reynolds:

Iam writing to you for information in regards to the injection of FORMADEHYDE directly into my veins. As you know I spoke to you about the dialyzer and I did look up the USC and I did learn the meaning of the numbers. I am a dialysis patient of 12 years, I have never re-used a dialyzer in all of that time. My doctors openly tell me that if they go to re-use that I will be getting a dose of formadehyde three times a week, each dose will be 5 ppm. I am asking you through the freedom of information act the following. Is the direct injection of formaldehyde approved for human beings? Since this is being done to thousands of patients every other day for the rest of their life I am sure that you must have some information on the injection of this disinfectant. I am pleading with you for my very life, my doctor told me that it is not safe but my unit is looking into doing it, if I am to make an educated decision on whether to re-use or not to re-use I feel this information is absolutely imperative. Your immediate attention to this matter will be most appreciated, my life is on the line.

I am enclosing an article for you to read about this dreadful situation.

Sincerely,
Robert Rosen
Robert Rosen

c.c. Herb Denenberg T.V. 10

P.S. I beleive I requested this information some time ago and I never received an answer, my time is running out. Please remember that the only people that are injected with formadehyde are dead people and dialysis patients.

NAPHT
NATIONAL ASSOCIATION OF PATIENTS ON
HEMODIALYSIS AND TRANSPLANTATION, INC.

156 William St., New York, N.Y. 10038
(212) 619-2727

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Harlem Hospital

Mr. Robert Rosen
6332 Powder Horn Court
Bensalem, PA 19020

September 21 1982

Dear Mr. Rosen:

Thank you very much for sending me the articles in the Bucks County Courier Times of September 2, 1982. I give you a lot of credit for standing up for your right to informed consent concerning reuse.

As you know NAPHT has been opposed to re-use. On a personal basis I have recognized that over 30% of the dialysis units now re-use, and the government continues to refrain from legislating or regulating medical practice. Therefore I, like yourself have attempted to learn a great deal about formaldehyde and re-use. I have also participated in working groups which have been developing standards for re-use, with hopes that my concerns will at least be included in standards or guidelines for the benefit of patients. You might ask the local Kidney Foundation for its "Interim Guidelines on Re-use." They are not what patients ideally want, but do include testing for formaldehyde and informed consent.

The issue can only be resolved in two ways: 1) A long term study identifying the toxic level of formaldehyde in primates. (No one is really working on this now). 2) A court case where re-use is either banned, or informed consent is required, and if the patient refuses he must either be given a new, comparable dialyzer each time, or placed in a unit which does not re-use and provides comparable quality care near his home.

If you are looking into the legal possibilities for a court case you might contact a lawyer by the name of Norman Landau (233 Broadway, New York, New York 10279, tel. 212-962-7545). I understand from a friend, Dr. Jay Meltzer (a nephrologist) that Mr. Landau has handled a number of malpractice suits for patients. I don't think he has handled any dialysis or re-use cases. It would be worth calling or writing him to learn what you can.

Do keep me posted and let me know if I can be of assistance to you. Best wishes.

Sincerely,

John Neumann
John Newmann, President

A NON PROFIT ORGANIZATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

OCT 22 1982

Mr. Robert Rosen
6332 Powder Horn Court
Bensalem, Pennsylvania 19020

Dear Mr. Rosen:

This letter is in response to your letter addressed to "To Whom It May Concern" dated July 31, 1982, and to your letter to Mr. Reynolds of September 20, 1982.

In both letters you express your concern about the use of formaldehyde for the disinfection of a dialyzer prior to use in humans. Specifically, your doctors have informed you that, as a dialysis patient treated with dialyzers reprocessed for reuse, you may be getting a dose of 5 ppm of formaldehyde solution at each dialysis session. You also requested information related to the safety of a human receiving such a trace amount of formaldehyde during dialysis.

Most individuals are chronically exposed to formaldehyde, which is a natural product found in many foods and water in trace amounts. In the human body it is rapidly transformed into formic acid, which is in turn transformed into carbon dioxide and water which are normal metabolic products. Part of the formic acid is normally excreted in the urine. The urine of normal unexposed individuals has an average content of 17 ppm of formic acid. In the case of patients with chronic renal insufficiency, the formic acid and formaldehyde molecules would quickly pass through the dialysis membranes.

Formaldehyde is used as an ingredient in numerous products regulated by the Food and Drug Administration (FDA). For example, it is used in several vaccines to inactivate viruses and bacteria and to detoxify bacterial toxins, in a number of drug and dental products, and as a preservative in food processing.

Formaldehyde solutions have been used for the disinfection of dialyzers for many years. In fact, some dialyzers were, until recently, sold containing a formaldehyde solution as a disinfectant. These devices were in commercial distribution prior to the enactment of the Medical Device Amendments on May 28, 1976. Thus, dialyzers disinfected with formaldehyde solutions may be legally marketed in the U.S. The FDA is unaware of any report of adverse reactions due to the long-term use of dialyzers disinfected with formaldehyde solutions.

Detection of formaldehyde has been improved significantly over recent years. Present methods permit the relatively simple routine detection of formaldehyde down to 5 ppm. More sophisticated methods can detect it at much lower levels. It is likely that prior to the development of these new detection methods, patients being dialyzed with dialyzers disinfected with formaldehyde solutions were exposed to levels of formaldehyde several times greater than the low levels achievable today.

Most physicians agree that dialysis centers performing routine use of reprocessed dialyzers should maintain careful control of their procedures. Routine testing for residual formaldehyde could ensure that this level is less than 5 ppm. However, appropriately validated methods for rinsing dialyzers prior to use can achieve significantly lower levels of residual formaldehyde.

We trust that this information will help you in making an educated decision on whether or not to allow yourself to be treated with reused dialyzers.

If you have any further questions, please call me at (301) 427-7750.

Sincerely yours,

Fernando Villarroel, Ph.D.
Director
Division of Gastroenterology-Urology
and General Use Devices
Office of Medical Devices
National Center for Devices
and Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administratio
Rockville MD 20857

DEC 7 1982

The Honorable James J. Rhoades
Senate of Pennsylvania
Room 205, City Hall
Pottsville, Pennsylvania 17901

Dear Senator Rhoades:

This is in response to your letter of November 1 to Secretary Schweiker concerning Mr. Robert Rosen, a dialysis patient who is a resident of Bensalem, Pennsylvania. Mr. Rosen has written to us before about the use of formaldehyde as a disinfectant in preparing dialyzers for re-use. For your information, I am enclosing a copy of his earlier letter and our response.

Mr. Rosen raises two separate issues in his letters: whether the use of formaldehyde for disinfecting dialyzers is safe, and whether the re-use of dialyzers violates FDA regulations.

Let me address the formaldehyde safety issue first. Formaldehyde has not been shown to be toxic when ingested or injected in trace amounts. In fact, minute quantities of formaldehyde are used in several vaccines approved by the Food and Drug Administration to inactivate viruses and bacteria, in a number of drug and dental products, and as a preservative in food processing. I should also note that formaldehyde has been used to disinfect dialyzers for many years.

The key factor in the question of safety, of course, is the amount of formaldehyde to which the patient is exposed. Thus it is very important that the formaldehyde used for disinfection be thoroughly removed before the dialyzer is used again. The guidelines for disinfection of dialyzers issued by the National Kidney Foundation are very explicit on this point; they specify that the formaldehyde remaining after the disinfection process should be no more than 5 parts per million, and that documentation that the formaldehyde has been removed to this level is mandatory. (I might also mention that because formaldehyde's half-life in blood is very short, and because of the dilution of the dialyzer fluid with the patient's blood, the actual concentration of formaldehyde in the blood would be well below 0.5 parts per million even if the concentration in the dialyzer liquid were as high as 10 parts per million.)

There is no clinical evidence that formaldehyde in concentrations at or below the Kidney Foundation's guideline level are harmful to dialysis patients. In fact, I understand that roughly one-third to one-half of dialysis patients in the United States are now being treated with re-used dialyzers, and that the percentage is even greater in England. It is also interesting to note that patients in the early years of dialysis, when techniques for measuring traces of formaldehyde were not as refined as they are today, probably were exposed routinely to concentrations on the order of 25 parts per million without apparent effect.

Mr. Rosen has also expressed concern at the stipulation in the Kidney Foundation's guidelines that hospital personnel sterilizing dialyzers be properly protected from the formaldehyde they may be using, in accordance with regulations of the Occupational Safey and Health Administration (OSHA). The reason for the protection of hospital personnel is that they are working with much higher levels of formaldehyde than dialysis patients could receive. They are sterilizing the device with strong formaldehyde solutions, while the patient is exposed only to the trace amounts of formaldehyde left after the disinfectant is removed.

Finally, let me address the FDA labeling issue. We require that the manufacturers of devices such as dialyzers specify the intended use, e.g., for one-time or re-use, in their labeling. Most manufacturers have chosen to label dialyzers marketed in the United States "for one-time use only." If a physician wishes to follow a procedure different from that specified in the labeling, he or she must assume the responsibility for the safety and effectiveness of this use.

I hope this has been helpful to you and to Mr. Rosen. Please let me know if I can be of further service.

Sincerely yours,

John C. Villforth
Director
National Center for Devices
and Radiological Health

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

HEALTH CARE FINANCING
ADMINISTRATION

The Administrator
Washington, D.C. 20201

Dec. 1982

The Honorable James K. Coyne
House of Representatives
Washington, D.C. 20515

Dear Mr. Coyne:

This is in response to your recent letter to Secretary Schweiker on behalf of your constituent, Mr. Robert Rosen of Bensalem, Pennsylvania.

Multiple use of hemodialyzers has been an ongoing practice in dialysis units in this country and in many parts of Europe for 20 years. According to a 1981 survey, 18 percent of Medicare dialysis facilities reported that they reuse dialyzers. This practice has received a great deal of attention in both the professional literature and conference agendas of the renal community. Many articles have stated that there would be potential cost savings to the Medicare program if dialyzers were used more than once. Others have raised questions about the appropriateness of dialyzer reuse. There is no Medicare policy that requires dialyzer reuse. In recognition of the difficulties facing those who must make decisions on this subject, Congress called for a study of the medical appropriateness and safety of cleaning and reusing dialyzers in June of 1978.

In response to the wishes of Congress, the National Institutes of Health (NIH) conducted a study on reuse of hemodialyzers and concluded that hemodialyzers can be reused if they are reprocessed in accordance with certain procedures. There are also several attempts underway by the renal community to establish procedures for the processing of dialyzers in ways that will guarantee the safety of patients if their treatment involves multiple use of dialyzers. Additionally, the Food and Drug Administration does not officially require the "one time use only" label to be placed on hemodialyzers.

It appears from your inquiry that Mr. Rosen is unclear about a patient's right to accept or refuse reused dialyzers. The regulations governing the End-Stage Renal Disease (ESRD) Program require that all patients have the opportunity to participate in the planning of their medical treatment. In addition, patients being treated by a particular ESRD facility may be transferred or discharged only for medical reasons or for the patient's welfare or that of other patients, or for nonpayment of fees (except as prohibited by Title XVIII of the Social Security Act).

Mr. Rosen may wish to discuss this issue, and the other medical issues he raised, with the physicians at the facility where he is currently receiving dialysis treatments. In addition, he may wish to contact Mr. Ronald Wrona, Executive Director, ESRD Network 24 at 1003 W. 9th Avenue, Suite H, King of Prussia, Pennsylvania 19406, telephone (215) 265-1101.

Sincerely yours,

Carolyne K. Davis, Ph.D.

ROUTING AND TRANSMITTAL SLIP Date 12-20-82

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. Jim Benson		
2. Bob Wetherell		
3. Fernando Villarroel, HFK-420, SSP 1442A		
4. Al Duncan		
5.		

	Action		File		Note and Return
	Approval		For Clearance		Per Conversation
	As Requested		For Correction		Prepare Reply
	Circulate	XXX	For Your Information		See Me
	Comment		Investigate		Signature
	Coordination		Justify		

REMARKS

FYI--Dr. Hayes will discuss with Dr. Brandt.

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
Dan Brand, Executive Secretariat	14-85
	Phone No. 35004

5041-102
☆U.S. G.P.O. 1977-241-530/3090

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

December 13, 1982

Commissioner of Food and Drugs

Reuse of Dialysis Equipment

Assistant Secretary for Health
Through: ES/PHS______________

PURPOSE

This memorandum is intended to summarize FDA's involvement in reusable dialysis equipment, and to brief you on my plans to organize a Departmental group to coordinate the development of an HHS position on the use of such equipment.

BACKGROUND

Under current legislation, the Department of Health and Human Services is obligated to pay the cost of renal dialysis in the End Stage Renal Disease (ESRD) Program. The number of persons in the program is currently 63,214, which will cost $1.8 billion to cover 87,000 patients. The high costs have prompted examinations of ways to reduce the cost for dialysis treatment, one being the multiple use of dialysis filters.

FDA Involvement in Dialysis Treatment

Currently, all dialyzer filters sold in the United States are labeled "for single use only." However, approximately 30-50 percent of these filters are reprocessed for reuse. FDA is involved in their use and reuse in three ways:

- Manufacturers will soon be submitting, for Agency approval, dialyzer filters labeled for multiple use.
- Automatic machines specially designed for reprocessing filters have been authorized for marketing under Section 510(k) of the Food, Drug and Cosmetic Act.
- FDA has participated in and financially supported workshops for the purpose of developing guidelines for reprocessing dialysis filters. Drafts of these guidelines are now being reviewed by the Agency.

OTHER DHHS INVOLVEMENT

In 1978, Congress mandated a study of the medical appropriateness and safety of cleaning and reusing dialysis filters. A number of agencies within the Department are responsible for implementing that legislation.

- o The National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases has contracted with the Manhatten Kidney Center to evaluate the safety and effectiveness of cleaning and storage procedures for multiple use of dialysis filters. However, no clinical trials to determine the effects of filter reuse were included in the study.

- o HCFA has recently convened a department-wide work group to address the need for clinical studies and has prepared options suggesting ways to improve the ESRD Program's management. Those options included a recommendation that FDA conduct a clinical trial to evaluate dialysis filter reuse. Although we concur in the need for an evaluation, this Agency is not staffed and equipped for clinical research. We can, however, recommend protocols for such research and review the data from clinical trials for adequacy.

The Next Step

Since other groups within the Department have become involved in dialysis filter reuse, I would like to organize a group to coordinate our efforts. Therefore, I would like to include this as a topic for our one-on-one meeting on December 14.

Arthur Hull Hayes, Jr., M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

[redacted]

ATTACHMENT B

Dec. 14, 1982

MEMORANDUM TO: The Executive Secretary
ATTN: Jacquelyn White

SUBJECT: Report of the Interdepartmental
Work Group on End-Stage Renal Disease —— NON-CONCUR

FROM: Dale W. Sopper /s/ Dale W. Sopper
Assistant Secretary for
Management and Budget

I do not concur with forwarding this paper to the Secretary. Although I do not disagree with the general direction of the recommendations contained in the subject report, I must point out that this paper is incomplete and fails to respond to the Secretary's request of April 1982 for an ESRD options paper.

On April 8, the Secretary met with Dr. Davis to discuss ESRD issues and review the report completed by the Interdepartmental Work Group in December 1981. At the conclusion of the meeting, the Secretary asked HCFA to submit an abbreviated options paper to him by April 23, setting out alternative approaches to six major ESRD issues. In the paper, HCFA was to define resource requirements as well as expected benefits from the alternative approaches to each of these issues and state its recommendation for dealing with each issue.

I am concerned that HCFA appears to have developed its recommendations in the subject issue paper without attention to their potential budgetary impact. I propose that HCFA gather cost estimates for the recommendations from the agencies (including PHS, SSA and the Department of Education) which would be responsible for implementing them. As requested by the Secretary on April 8, HCFA should revise the paper to include these cost estimates as well as the benefits expected for implementing the alternative approaches. I suggest further that HCFA submit these cost estimates for review by my budget staff for conformance with the Department's FY 1983 and FY 1984 budgets before HCFA again submits this paper to the Secretary for decision.

8th District, Pennsylvania

119 Cannon House Office Building
Washington, D.C. 20515
202-225-4276

District Offices:
Doylestown 215-345-4040
Oxford Valley 215-752-5000
Hatboro 215-441-8454

Banking, Finance and
Urban Affairs

House Administration

Joint Committee on
Museums and Libraries

CONGRESS OF THE UNITED STATES
HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515

December 14, 1982

Mr. Robert Rosen
6332 Powder Horn Court
Bensalem, Pennsylvania 19020

Dear Mr. Rosen:

I have enclosed for you the response I received from Carolyne K. Davis of the Health Care Financing Administration regarding our inquiry about hemodialyzers.

As you can see, **according to the National Istitutes of Health, the hemodialyzers can be reused if they are reprocessed in accordance with certain procedures.** I recommend that you discuss the reprocessing procedure used by the University of Pennsylvania with your doctor and contact Mr. Ronald Wrona (as suggested in Dr. Davis' letter) to ensure the safety of that procedure.

It appears that the reuse of dialyzers is still of questionable safety. I am writing to Secretary Schweiker once again to request that another, more definitive study of this problem be made so that those people, like you, whose lives depend on this process can be sure of the safety of the equipment being used.

Please contact me if I can be of any further help to you.

Sincerely,

James K. Coyne
Member of Congress

JKC:ja
Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES
Health Care Financing Administration

6325 Security Boulevard
Baltimore, MD 21207

JAN 6 1983

FT-22

Mr. Robert Rosen
6332 Powder Horn Court
Bensalem, Pennsylvania 19020

Dear Mr. Rosen:

This is in response to your recent letter concerning the reuse of hemodialyzers.

Multiple use of hemodialyzers has been an ongoing practice in dialysis units in this country and in many parts of Europe for 20 years. According to a 1981 survey, 18 percent of Medicare dialysis facilities reported that they reuse dialyzers. This practice has received a great deal of attention in both the professional literature and conference agendas of the renal community. Many articles have stated that there would be potential cost savings to the Medicare program if dialyzers were used more than once. Others have raised questions about the appropriateness of dialyzer reuse. There is no Medicare policy that requires dialyzer reuse. In recognition of the difficulties facing those who must make decisions on this subject, Congress called for a study of the medical appropriateness and safety of cleaning and reusing dialyzers in June of 1978.

In response to the wishes of Congress, the National Institutes of Health (NIH) conducted a study on reuse of hemodialyzers and concluded that hemodialyzers can be reused if they are reprocessed in accordance with certain procedures. There are also several attempts underway by the renal community to establish procedures for the processing of dialyzers in ways that will guarantee the safety of patients if their treatment involves multiple use of dialyzers. Additionally, the Food and Drug Administration does not officially require the "one time use only" label to be placed on hemodialyzers.

It appears from your letter that you are unclear about a patient's right to accept or refuse reused dialyzers. The regulations governing the End-Stage Renal Disease (ESRD) Program require that all patients have the opportunity to participate in the planning of their medical treatment. In addition, patients being treated by a particular ESRD facility may be transferred or discharged only for medical reasons or for the patient's welfare or that of other patients, or for nonpayment of fees (except as prohibited by Title XVIII of the Social Security Act).

You may wish to discuss this issue, and the other medical issues you raised, with the physicians at the facility where you are currently receiving dialysis treatments. In addition, you may wish to contact Mr. Ronald Wrona, Executive Director, ESRD Network 24 at 1003 West Ninth Avenue, Suite H, King of Prussia, Pennsylvania 19406, telephone (215) 265-1101.

Sincerely yours,

Larry A. Oday

Larry A. Oday
Director
Bureau of Program Policy

JAN 6 1983

6325 Security Boulevard
Baltimore, MD 21207

FT-22

Honorable Arlen Specter
United States Senate
Washington, D.C. 20510

Dear Senator Specter:

This is in response to your inquiry on behalf of Mr. Robert Rosen of Bensalem, Pennsylvania. We are writing directly to Mr. Rosen in response to his letter to the President.

Multiple use of hemodialyzers has been an ongoing practice in dialysis units in this country and in many parts of Europe for 20 years. According to a 1981 survey, 18 percent of Medicare dialysis facilities reported that they reuse dialyzers. This practice has received a great deal of attention in both the professional literature and conference agendas of the renal community. Many articles have stated that there would be potential cost savings to the Medicare program if dialyzers were used more than once. Others have raised questions about the appropriateness of dialyzer reuse. There is no Medicare policy that requires dialyzer reuse. In recognition of the difficulties facing those who must make decisions on this subject, Congress called for a study of the medical appropriateness and safety of cleaning and reusing dialyzers in June of 1978.

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Sincerely yours,

Larry A. Oday
Director
Bureau of Program Policy

Enclosure:
Constituent's correspondence

FEB 11, 1983

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

End-Stage Renal Disease

Agency Heads
OASH Staff Offices

End-Stage, Renal Disease (ESRD) affects a large number of people in the United States and accounts for much human suffering as well as great cost (nearly $1.8 Billion in 1982). A departmental task force has made several recommendations for approaching this problem, and the PHS has been assigned responsibility for most of them. I find them to be both reasonable and appropriate. A copy of the report is attached.

It is critical that we have a coordinated response to these recommendations. Accordingly, I am designating NIH as the lead Agency to provide me with this response. I have asked Dr. James Wyngaarden to establish a Coordinating Committee to oversea this effort. The Committee will consist of a representative from each agency; Dr. Wyngaarden will appoint the chairman. Please advise him of your representative within one week. The Committee will meet at the call of the chairman.

My preliminary assignment for each of the recommendations is listed below:, however, this assignment may be modified by the Coordinating Committee.

Recommendation #2:

Part 1: OASH-DPHP with representatives of all agencies.
Part 2: NIH with representatives of NIADDK , NIAID and NHIBI.

Recommendation #3:

NIH

Recommendation #4:

Transplantation: NIH
Dialyzer Reuse: FDA

I look forward to your active participation in this important effort.

Attachment

JFD:mas:1/19/83

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 15 1983

The Honorable Arlen Specter
United States Senate
Washington, D.C. 20510

Dear Senator Specter:

This is in further response to your letter of February 18, 1983, on behalf of Mr. Robert Rosen of Bensalem, Pennsylvania.

Mr. Rosen raises two separate issues pertinent to the Food and Drug Administration (FDA): whether the use of formaldehyde for disinfecting dialyzers is safe, and whether the reuse of dialyzers violates FDA regulations.

Let me address the formaldehyde safety issue first. Formaldehyde has not been shown to be toxic when ingested or injected in trace amounts. In fact, minute quantities of formaldehyde are used in several vaccines approved by FDA to inactivate viruses and bacteria, in a number of drug and dental products, and as a preservative in food processing. It should also be noted that formaldehyde has been used to disinfect dialyzers for many years.

The key factors in the question of safety, of course, is the amount of formaldehyde to which the patient is exposed, and the manner by which it enters the body. Thus, it is very important that the formaldehyde used for disinfection be removed thoroughly, before the dialyzer is used again. The guidelines for disinfection of dailyzers issued by the National Kidney Foundation (NKF) are very explicit on this point. They specify that the formaldehyde remaining after the disinfection process should be no more than 5 parts per million, and that documentation of the removal of formaldehyde to this level is of the utmost importance.

The half-life of formaldehyde in blood is very short, and due to the dilution of the dialyzer fluid with the patient's blood, the actual concentration of formaldehyde in the blood would be well below 0.5 parts per million even if the concentration in the dialyzer liquid were as high as 10 parts per million.

Finally, let me address the issue of the label on a dialyzer and the manner in which the dialyzer is used. We require that the manufacturers of devices such as dialyzers specify the intended use, e.g., for one time or for reuse, in their labeling. Most manufacturers have chosen to label dialyzers marketed in the United States "for one time use only." If a physician wishes to follow a procedure different from that specified in the labeling, he or she may do so but must assume the responsibility for the safety and effectiveness of this use.

I hope this has been helpful to you and to Mr. Rosen. If I can be of any other assistance, please let me know.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

Enclosure
Constituent's ltr

C. Dialyzer Reuse

Introduction.

The ESRD community is currently divided on the issue of whether it is safe to reuse dialyzers, which is one way a facility can reduce per treatment costs. In the NPRM, we explained that we were neutral on this issue; we are neither supporting nor prohibiting it in these final regulations.

Comment: Some commenters stated that, in order to increase efficiency and reduce costs, facilities should reuse dialyzers.

Response: We have no authority to require reuse. However, if a facility decides to reuse dialyzers, it will retain the savings from that practice.

Comment: Other commenters claimed that reuse is unproven and unsafe. It was also noted that some States have constraints on reuse.

Response: HCFA is neutral on reuse. Reuse is prevalent in Europe and many facilities in the United States reuse. Preliminary studies show that reuse is successful where it is done properly. Nevertheless, we do not presently require or prohibit reuse. We will continue to study dialyzer reuse, and to monitor outcomes of those facilities that reuse dialyzers, in order to determine whether we should revise the program's health and safety, as well as reimbursement, requirements with respect to dialyzer reuse.

Comment: Some commenters suggested that we set as separate payment rate for facilities that reuse dialyzers.

Response: We set composite rates based on the audits of randomly selected facilities. Twenty-five percent of the independent facilities in the audits reused dialyzers, and their costs were included in setting the rates. We cannot set separate rates for reuse because this would be impractical, since some patients in a facility may reuse, and some may not. In addition, some facilities may choose to use the savings from reuse to offset some other excessive cost in their operation. Under the prospective reimbursement system, we do not intend to adjust individual facilities' rates to their actual costs, because this removes the incentive to be efficient.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Villarroel

Memorandum

Date . JUL 6 1983

From Assistant Director for Education and Communications

Subject Meeting of NCDRH working group on dialyzer reuse, July 1, 1983

To Director, NCDRH
Deputy Director, NCDRH

This is to summarize the consensus which emerged from the above meeting, and to offer suggestions on a future course of action.

Briefly, the working group agreed on the following points.

- It is granted that we do not have a definitive answer to the question of long-term risks from dialyzer reuse. On the other hand, there may be risks from single use, which are also unknown. Given the fact of ever-increasing reuse, and the encouraging lack of evidence of short-term ill effects from studies to date, we should proceed to investigate the need for and possibly develop guidelines on reuse procedures.

- The need for guidelines is presumptive; that is, we do not have evidence that poor reuse practices are necessarily occurring, or that the reuse practices of some institutions are inadequate. But with more and more facilities turning to reuse, some sort of nationally recognized protocol for how to safely re-use should be helpful. At the least, it will push those facilities at the "trailing edge" of practice to improve their procedures (not unlike the effect of quality assurance programs in the x-ray area).

- Guidelines will have other beneficial spinoffs. They will provide assurance to patients and organized patient groups that the government has studied the matter and has endorsed certain principles and/or procedures as adequate. Note, too, that patient organizations, as well as key medical organizations, must play an active role in developing/endorsing the guidelines. Once the guidance is widely published, patient groups may act to ensure that individual facilities are following the prescribed procedures (in principle, not unlike the mammography patient asking the physician about radiation equipment and doses, except that dialyzer patients are better organized to exert pressure). This in itself can help to improve "trailing edge" facilities. Medicolegal considerations, too, may exert pressure on below-par facilities to improve, since the guidelines may become the accepted "standard of practice."

- The best way to develop the guidance will be through a joint NIH-FDA Consensus Development Conference. This vehicle will provide maximum visibility, assure the participation of the right groups, and provide the proper "imprimatur" for the guidelines. Conferees should deal not only with the development of the guidelines themselves, but also with the important issues of long-term risk (do we know enough to develop guidelines?), the need for the guidance, and the question of which patients, if any, should not reuse.
- The desirability of the conference should be expressed to the PHS Coordinating Committee. Dr. Villarroel will therefore submit to Dr. Salens the attached "FDA Recommendation to the PHS Coordinating Committee," which was reviewed and approved by the working group.
- Regarding the conference which Si Perry has proposed at Georgetown, FDA should be a co-sponsor, assuming that other groups have agreed to kick in as well. (Dr. Perry indicated that the National Nephrology Foundation and ECRI are potential co-sponsors.) The Perry conference will not directly overlap the NIH one, in that it will cover re-use issues in general rather than focus on dialyzers, and it will not develop any specific guidance.
- The proposal to develop and use a HCFA data base to further investigate outcomes among single-use vs reuse patients should be pursued. The NCDRH "team" to work with HCFA in planning the data base should include a dialysis expert and an epidemiologist/statistician.

Mark

Mark Barnett

Attachment

cc:
Senior Staff
Working Group members
  Mr. Arcarese
  Mr. Chantler
  Mr. Cotter
  Mr. Duncan
  Dr. Haffner
  Mr. Kobren
  Dr. Mohan
  Dr. Silverman
  Dr. Villarroel ✓

FDA RECOMMENDATION TO PHS COORDINATING COMMITTEE

The Committee notes that dialyzer reuse is already a widespread practice in the United States and abroad, and is continuing to increase. Experience to date indicates that the outcome of patients treated with dialyzers used multiple times is not significantly different from that of patients treated with dialyzers used only one time, but this is the case only when careful dialyzer reprocessing and preparation procedures are followed. Even in this case, the possibility of long-term effects, or very infrequent acute adverse effects, cannot be ruled out completely. In order to ensure that patients are protected from the adverse effects of inadequate dialyzer reprocessing, there is a need for consensus and guidance on the methodology of reprocessing. The PHS coordinating committee therefore recommends:

- o That NIH and FDA cosponsor a Consensus Development Conference to include the following objectives:
  - to assess dialyzer reprocessing procedures available today, including personnel, quality assurance, record keeping, and the need for guidelines in these areas.
  - based on this assessment, to recommend guidelines for the reprocessing of dialyzers if needed, including an identification of those patient groups where reuse may be contraindicated.
  - to recommend future research and development in order to improve the safety of dialyzer reprocessing.

- o In conjunction with the implementation of recommendation No. 1 — that HCFA be authorized to implement a comprehensive departmental ESRD data base — PHS, including FDA, NIH & CDC, should initiate a program to compare ~~evaluate~~ the outcome of patients treated with dialyzers treated one time and multiple times. This program should be extended for a period no less than 5 years and should include data on mortality and morbidity of ESRD patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Administration

Regional Office VI
1200 Main Tower Building
Dallas, Texas 75202

23 AUG 1983

Mr. Robert D. Rosen
6332 Powder Horn Court
Cornwells Heights, Pennsylvania 19020

Dear Mr. Rosen:

This is in further response to your letter of August 1 requesting information about reports of deaths of several dialysis patients in Baton Rouge, Louisiana.

The enclosed article from the May 13, 1983 Mortality and Morbidity Weekly Reports, published by the Center for Disease Control in Atlanta, Georgia, contains information about the investigation of an outbreak of infections that affected a number of patients of two Baton Rouge renal dialysis facilities. We trust this information will be helpful to you.

If the Regional Office can be of further assistance, please let me know.

Sincerely,

for
J. D. Sconce
Regional Administrator

Enclosures

From MMWR—Morbidity and Mortality Weekly Report
May 13, 1983; Vol. 32, No. 18, pp. 244–245
Presented in its entire verbatim form

NONTUBERCULOUS MYCOBACTERIAL INFECTIONS IN HEMODIALYSIS PATIENTS— LOUISIANA, 1982

Between April 16 and October 8, 1982, 27 cases of nontuberculous mycobacterial (NTM) infection were identified among 140 patients with end-stage renal disease undergoing outpatient hemodialysis therapy in two centers of a dialysis corporation in Louisiana. The organisms isolated from 24 of these patients have been identified as *Mycobacterium chelonei* subspecies *abscessus*, while that isolated from one patient has been identified as an *M. chelonei*-like organism. The isolates from the remaining two patients have not yet been speciated. Sixteen patients were male. Age ranged from 29 to 81 years (mean 58 years). All 27 patients were dialyzed for 4 hours a day, 3 times a week; 21 at dialysis center A and 6 at dialysis center B. Attack rates were equal in the two dialysis centers, with an overall attack rate of 19%.

A wide spectrum of illness was seen. Eighteen patients had bacteremia, and four had localized infections—three with soft tissue abscesses and one involving an access graft. Five patients had positive cultures from multiple sites, including blood, skin nodules, bone marrow, and hemodialysis grafts. In general, the clinical syndrome associated with isolated NTM bacteremia was characterized by vague constitutional symptoms and low-grade fever; three patients were asymptomatic. Thirteen patients with multiple underlying medical problems have since died; the extent to which their deaths were due to their infections is unknown.

A case-control study was undertaken to identify possible risk factors for the development of NTM infection in hemodialysis patients. Case and control patients were similar in age, sex, and racial distribution. Preliminary results of the epidemiologic investigation did not identify any one risk factor to account for the outbreak. Type of access graft used and hospital in which the graft was inserted did not differ between cases and controls. Exposure to a given dialysis station or a particular type of dialyzer (artificial kidney) was not associated with an increased risk of infection. However, one factor common to all patients and, therefore, not examined in the case-control study was exposure to processed dialyzers.

All dialyzers used in both centers were processed routinely in dialysis center A before use. The processing procedure included rinsing with water and disinfecting with 2% aqueous formaldehyde for a minimum of 24 hours. Some, but not all, patients reused their dialyzers one or more times. To standardize procedures in the dialysis center and to prevent the "new dialyzer syndrome", the same procedure was used to process new dialyzers for single use and previously used dialyzers, for reuse. Four of 10 patients positive for hepatitis B surface antigen, who did not reuse dialyzers, were found to have NTM infections.

Extensive environmental sampling showed NTM in water samples from multiple sites in both dialysis centers, including water used to rinse dialyzers before the disinfection procedure, to prepare the 2% formaldehyde solution used in the disinfection procedure, and to prepare dialysis fluids. While all the environmental isolates have not been speciated, both *M. chelonei* subspecies *abscessus*, and *M. chelonei*-like organisms, along with other NTM were present in the water. In addition, NTM (speciation pending) were present in the blood compartment (patient side) of five of 31 dialyzers sampled after the routine disinfection procedure. The formaldehyde concentration in two of three culture-positive dialyzers tested was less than 2% which is the concentration routinely used for disinfection.

Preliminary laboratory studies indicate that, while the patient isolates of *M. chelonei* subspecies *abscessus* tested to date do not survive exposure to 2% formaldehyde for 24 hours, the single *M. chelonei*-like organism recovered from one patient does survive such exposure. No isolates survived exposures to 4% formaldehyde for 24 hours.

In both centers, dialyzer reuse was discontinued and environmental control procedures, including disinfecting the water-treatment systems, were instituted. No new cases of NTM infection have been identified in 34 patients who began dialysis after these interventions.

Editorial Note: *M. chelonei* and *M. chelonei*-like organisms are rapidly growing mycobacteria frequently found in soil and water.[1] Recently, their role in human illness has been recognized with increasing frequency in many different clinical settings. *M. chelonei* has been reported to cause abscesses, cutaneous and lymphatic infections, pulmonary infections, post-operative wound infections, prosthetic-valve endocarditis, thyroiditis, osteomyelitis, arthritis, and ocular infections, while *M. chelonei*-like organisms have been associated with peritonitis in peritoneal dialysis patients.[2] Although these infections are usually localized, disseminated disease has been reported among immunocompromised patients and in at least one hemodialysis patient.[3] Medical treatment of such infections is often difficult, particularly for patients with disseminated disease, because the organisms are usually resistant to most antimicrobials.

The source of NTM infection in this outbreak was probably the water used in processing the dialyzers. The design of the water treatment system in this center may have led to high concentrations of these organisms in the water used to process the dialyzers, and inconsistencies in the subsequent disinfection procedures may have resulted in incomplete eradication of NTM from the dialyzers. Patients may then have become infected when their blood circulated through processed dialyzers containing viable NTM.

While a survey of reference laboratories has not identified any other clusters of NTM infections in hemodialysis patients, there is reason for concern that such infections may occur elsewhere. These organisms are known to grow in potable water and, consequently, may be found in water used in hemodialysis centers. Furthermore, standard plate-count methods for monitoring water quality in dialysis centers may not detect this type of contamination. In addition, previous studies have shown that, in comparison with the gram-negative species frequently found in water, NTM—especially *M. chelonei*-like organisms—can be relatively resistant to germicides.[4] Further studies to evaluate factors that may affect eradication of these organisms in dialyzers are in progress.

At present, dialysis center staffs should ensure that protocols for disinfection of dialyzers be followed rigorously, with particular attention to concentrations of germicides and contact time used. Physicians and dialysis center staffs should also be alert to the possible existence of NTM infection in hemodialysis patients, particularly because such infections may result in minimal, nonspecific symptoms. All hemodialysis patients with signs or symptoms of infection, especially those with unexplained fever, should have appropriate cultures taken. Because growth of NTM from clinical specimens may not be evident before 14 days, cultures should be held for at least this period before being reported as negative, and all isolates should be examined with stains for acid-fast organisms. NTM infections among dialysis patients should be reported to appropriate health departments to facilitate further evaluation of the epidemiology of such infections and to assist in the development of appropriate control measures. ☐

Reported by JW Brown III, T Cocke, M Marionneaux, Dept of Medicine, Louisiana State University, Baton Rouge, LM MacFarlan, H Bradford, C Caraway, Louisiana State Dept of Health and Human Resources; Respiratory and Special Pathogens Epidemiology Br, Respiratory and Special Pathogens Laboratory Br, Div of Bacterial Diseases, Div of Hepatitis and Viral Diseases, Center for Infectious Diseases, CDC.

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1 Wolinsky E. Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 1979;119:107-59.
2 Band JD, Ward JI, Fraser DW, et al. Peritonitis due to a *Mycobacterium chelonei*-like organism associated with intermittent chronic peritoneal dialysis. J Infect Dis 1982; 145:9-17.
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Memorandum

Date September 7, 1983

From Chairperson
Reuse Committe

Subject Minutes of Meeting

To Addressees

General Discussion

The first meeting of the cross-cutting committee on reuse of Medical Devices met on Tuesday, August 30, 1983. The main purpose of this meeting was to discuss what the responsibilities and the aims of the committee should be. It was agreed that with rising medical costs becoming an important issue, there is a greater probability that users of medical devices will be more likely to reuse them in order to cut costs. The committee agrees that reuse of disposable medical devices could have a major impact on the regulatory responsibilities of the NCDRH. The members of the committee suggests that it should begin an active study in this area to allow NCDRH to anticipate potential problems before they occur and make appropriate recommendations to the Director.

Topics discussed were:

1. Compliance Policy
   Does the FDA compliance policy guide on reuse of medical disposable devices need revision?

2. Hemodialysis
   Knowing that a great majority of hollow fiber hemodialyzers are being reused, is the labeling for these devices adequate?

3. Physician Guideling and/or Education
   If reuse of a device is a medical decision, does the FDA have authority to prepare guidelines for the physician? If not, who should? Should FDA, through a training and education program educate users of reused devices on the proper way to clean and sterilize devices? Do we try to influence physician organizations to develop guidelines? Do we give them the financial and scientific support in this endeavor?

4. Definition of Reuse
   What exactly is meant by reuse of a medical device? Does this term include surgical instruments which are routinely reused? Do we direct our efforts only towards those devices that are labeled "disposable one time use only" or look primarily at the device and how it is used regardless of its labeling? What kind of

devices are being reused? Do we in fact have a problem now?

What do we anticipate in the future?

5. Strategy Paper on Reuse
   Dennis Cotter has written a strategy paper on reuse of hemodialysis devices. He needs comments as soon as possible.

6. Reuse Conference
   Dr. Seymour Perry is planning a conference on reuse. He has had discussions with Mark Barnett regarding NCDRH support. Correspondence regarding this conference will be sent to the members of the committee.

Action Items

It was agreed that the following items will be worked on by the appropriate members prior to the next meeting:

1. Each member will attempt to write a definition for "reuse" as applied to medical devices. Comments will be coalated so that a final definition can be developed by the next meeting.

2. Comment are needed to Cotter's strategy paper on reuse of hemodialyzer. Comments are needed by as soon as possible. Phone replys will be acceptable.

3. A memo will be drafted for review by the committee, requesting the offices of the NCDRH (primarily ODE) to provide input to the committee with regards to determining what devices are now being reused or may be reused in the future, what risks are involved, and where are they being reused (hospital, home).

4. Dialogue with Dr. Perry regarding reuse conference will be continued.

5. Contact the chairperson of the sterilization cross-cutting committee and keep her informed of our activities.

6. Review PHS FY'84 resource targets to determine what PHS objective relate to this committee's activities.

Next meeting - September 14, 1983, 8:45 in room 416, Twinbrook.

Lawrence Kobren

Addressees:

Jim Chantler, HFK-116
Kathy Shanahan, HFK-117
Evelyn Gordon, HFX-4
Robert Skufca, HFK-141
Fernando Villarroel, HFK-420
Norman Welford, HFK-420
Nancy Leonard, HFX-18
Dennis Cotter, HFK-30
Norb Heib, HFK-300

cc: Linda Sudam
Virginia Ross
Charles Showalter
Robert Cangeloski

REUSE COMMITTEE

Minutes

Members

Jim Chantler	HFK-116
Kathy Shanahan	HFK-117
Evelyn Gordon	HFX-4
Robert Skufca	HFX-200
Fernando Villarroel	HFK-420
Norman Welford	HFK-420
Nancy Leonard	HFX-18
Norb Heib	HFX-460
Nancy Clements	HFX-460
Sally Hedrick	HFX-76

Subject - Minutes of Reuse Committee
Date: - October 3, 1983

Discussions

1. Dr. Villarroel briefed the Committee on the activities of the PHS ESRD Coordinating Committee. He indicated that the memo to Dr. Brant from the PHS Committee will endorse the concept of initiating a program using HCFA data to compare the outcome of patients treated with dialyzers one time and multiple times. The memo, however, will not include any recommendation concerning guidelines for reuse. The Committee agreed with this concept and suggested that someone from this Committee be assigned to any FDA/NCDRH team that would be involved in this study. The Committee believes that some NCDRH resources (manpower, or financial) will be necessary to support this effort and that the Director of the Division of Planning and Evaluation be made aware of this fact. (Copy of these minutes will be forwarded.)

2. Dr. Villarroel discussed plans to develop guidelines for the appropriate reprocessing procedures for dialyzers. I reported that Mr. Benson had assigned the Office of Training and Assistance the lead in getting these guidelines developed. Dr. Villarroel indicated that it was his opinion that the most effective way to get the guidelines developed was by using an outside contractor. He also indicated that he had begun to develop a statement of work to do this. The Committee agreed with this approach and asked Dr. Villarroel to continue his efforts. The members of the Committee wil expedite review of the document by working through their various offices in the center. The final work statement, representing input from all of the NCDRH offices will be forwarded to OTA (based on Mr. Benson's directive) for implementation.

3. The Committee reviewed the proposed in house Reuse inventory form for all devices. Some changes were suggested. I indicated I will discuss these changes with Dr. Evelyn Gordon and report back to the committee.

Action Items

1. Continue to develop Statement of Work for Reuse guidelines.

2. Revise Reuse Inventory Form

3. Review Reuse paper (prepared by D. Cotter) and be prepared to discuss the options outlined therein.

Next Meeting:

Date: October 24, 1983
Place: Twinbrook
Room: T-400
Time 9:30 AM

(REUSE-FORM TDM)

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases

Memorandum

Date October 5, 1983

From Chairman, PHS Coordinating Committee for
End Stage Renal Disease (ESRD)

Subject Report of Committee

To Assistant Secretary for Health
Through: Director, NIH ________
ES/NIH__________

Attached is the Report of the PHS Coordinating Committee for End Stage Renal Disease. As noted in Attachment C of the Report, this Committee was established by you on February 11, 1983 to develop a coordinated response to the recommendations contained in the February 1982 Report of the Intradepartmental ESRD Strategic Work Group.

I have chaired the PHS Coordinating Committee, which is comprised of representatives from NHLBI, NIADDK, NIAID, NIEHS, ADAMHA, CDC, FDA, and ODPHP. The Committee has met formally on May 24, June 20, and September 13. In addition, individual members have engaged in informal discussions as the need to address specific issues has arisen.

On behalf of the Committee, I am pleased to submit to you at this time our report and recommendations.

Lester B. Salans, M.D.
Director
National Institute of Arthritis,
Diabetes, and Digestive and Kidney Diseases

Attachment:

Report of PHS ESRD Coordinating Committee to
Assistant Secretary for Health

REPORT OF THE PHS ESRD COORDINATING COMMITTEE
TO THE ASSISTANT SECRETARY FOR HEALTH

October 1983

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VI. INTRADEPARTMENTAL ESRD STRATEGIC WORK GROUP RECOMMENDATION NO. 6--THAT PHS/FDA BE AUTHORIZED TO BEGIN CLINICAL TRIALS TO DETERMINE THE EFFECTS OF HEMODIALYZER REUSE:

The PHS Coordinating Committee does not agree with the ESRD Strategic Work Group recommendation that clinical trials on hemodialyzer reuse be initiated. This view is based on the fact that, since the original Work Group report advanced this recommendation approximately two years ago, considerable progress has been made in this area. For example, a National Workshop on Reuse of Consumables in Hemodialysis has found that dialysis using reprocessed consumables is clearly a widely accepted modification of standard treatment, and has generated reprocessing guidelines. A remaining issue, however, is the lack of systematic data on long-term morbidity or benefit in the reuse of dialysis consumables. To address this specific need, the PHS Coordinating Committee recommends that (1) HCFA should include information on dialyzer reuse in its comprehensive Departmental ESRD database described in the first recommendation of this report, and (2) that using this database, FDA initiate a study to compare the outcome of patients treated with dialyzers used once vs. multiple times. This study should be for a period of no less than five years and should include data on mortality and morbidity of ESRD patients. The Committee's views are detailed below.

The Committee notes that dialyzer reuse is now a widespread practice in the United States and abroad, and is continuing to increase. This is reflected in the Report of National Workshop on Reuse of Consumables in Hemodialysis sponsored by the Kidney Disease Coalition, March 1-2, 1982, in Washington, D.C. (Attachment J). Workshop participants included representatives from FDA, CDC, NIH and OASH, as well as experts from the academic and industrial communities. The Workshop Report notes that:

> "A great deal is known about reuse processes. A survey of active dialysis programs in 1978 indicated that over 15 percent of patients on maintenance hemodialysis were treated with reused dialyzers and a survey in 1981 indicated that percentage has risen above 27 percent. With such broad utilization, it is not experimental and is subject to legal and ethical assessment as therapy." (Attachment J, p.2)

The Report also contains helpful guidelines for dialyzer reuse entitled, Steps in Reprocessing of Dialysis Consumables (Attachment J. pp.A-1 to A-3).

It should be noted that CDC Hepatitis Laboratories have not issued formal guidelines or recommendations concerning the reuse of dialyzers since there is a general agency policy not to issue guidelines on reuse of disposable items. Nonetheless, since reuse of dialyzers is an established and commonly used technique, there have been publications to address how reuse can be dealt with and microbial hazards reduced. The methods identified by Dr. Norman Peterson (Attachment K) have been adopted by the National Kidney Foundation (Attachment L), which reviews and updates them annually. A letter (Attachment M) concerning some new revisions has been forwarded to the Kidney Foundation for its next revision.

Experience to date indicates that the outcome of patients treated with dialyzers used multiple times is not significantly different from that of patients treated with dialyzers used only one time, as long as careful dialyzer reprocessing and preparation procedures are followed. A remaining issue, however, is the long-term effects of dialyzer reuse. As noted in the Report of National Workshop on Reuse of Consumables in Hemodialysis: "There is no systematic data on long-term morbidity or benefit in the reuse of dialysis consumables" (Attachment J. p.B-1). The PHS Coordinating Committee recognizes that--even when careful dialyzer reprocessing and preparation procedures are followed--the possibility of long-term effects, or very infrequent acute adverse effects, cannot be ruled out completely. The Committee therefore recommends that FDA initiate a study to compare the outcome of patients treated with dialyzers used once vs. multiple times. This study should be for a period of no less than five years and should include data on mortality and morbidity of ESRD patients.

* * * * * * * * * * * * * * * * *

In conclusion, the PHS Coordinating Committee believes that the general response of the PHS to the Work Group's recommendations should be to maintain and enhance existing programs, many of which have made considerable progress in addressing ESRD issues since publication of the Report of the Intradepartmental ESRD Strategic Work Group in February 1982. On certain issues, such as dialyzer reuse, the PHS Coordinating Committee disagrees with the Work Group and has recommended a different course of action, in this case, a data analysis effort, rather than a clinical trial.

A summary of all the PHS Coordinating Committee's recommendations appears at the beginning of this report.

ATTACHMENTS

A - HCFA's Interpretive Summary of Intradepartmental ESRD Strategic Work Group Report and HCFA's Recommended Actions (November 2, 1982 Memorandum from HCFA Administrator to Secretary Schweiker).

B - Nonconcurrence with November 2, 1982, HCFA Memorandum (December 14, 1982 Memorandum from Assistant Secretary for Management and Budget to Executive Secretary).

C - Charge to the PHS ESRD Coordinating Committee (February 11, 1983 Memorandum from Assistant Secretary for Health to Agency Heads and OASH Staff Offices).

D - Membership of PHS ESRD Coordinating Committee.

E - Summary Recommendations Excerpted from Original Report of the Intradepartmental ESRD Strategic Work Group, February 1982.

F - NIH Definition of Prevention (May 9, 1983 Memorandum from NIH Coordinator for Disease Prevention and Health Promotion to Deputy Assistant for Health (DPHP).

G - Project-by-Project Listing of NIH FY 1982 Extramural Support of Prevention Research and Research Training Related to ESRD.

H - Excerpts from Report of NIH Coordinating Committee for Chronic Renal Disease.

I - List of Research Initiatives Identified in Report of Intradepartmental ESRD Strategic Work Group.

J - Report of National Workshop on Reuse of Consumables in Hemodialysis.

K - Microbiologic Hazards Associated with Reuse of Hemodialyzers.

L - Communication on Dialyzer Reuse from CDC to Vice President, National Kidney Foundation (May 23, 1983 Letter from Norman Petersen to David Ogden).

M - National Kidney Foundation Interim Standards for Reuse of Hemodialyzers (June 23, 1982 Memorandum from President, National Kidney Foundation, to Key Foundation Officials).

DEPARTMENT OF HEALTH & HUMAN SERVICES

ADVANCE

Refer to: FQA 4

Memorandum

Date:

From: Carolyne K. Davis, Ph.D. Carolyne K Davis
Administrator
Health Care Financing Administration

ATTACHMENT A

Subject: Report of the Intradepartmental ESRD Work Group

To: The Secretary
Through: US ____
ES ____

This memorandum summarizes the recommendations generated by the Intradepartmental End-Stage Renal Disease (ESRD) Work Group convened by the Health Care Financing Administration (HCFA) and describes the actions to be directed within the Department for implementation of these recommendations. These actions would require the submission of workplans within sixty days by the appropriate components and would be tracked by your Executive Secretariat.

The ESRD Work Group attempted to identify the essential issues relative to this program and develop a comprehensive strategy to improve ESRD Program management and the delivery of efficient, high quality, and cost effective health care.

Recommendation #1: DATA STRATEGY

Maintenance of a comprehensive Departmental data base composed of a basic patient registry and a facility specific cost/treatment data base.

Recommended Action: This task would be delegated to HCFA to carry out a redefinition of the ESRD data base to maximize its utility and accessibility. HCFA would be responsible for the maintenance of the basic patient data base and facility data base and would be available to support other Departmental components with special studies and research. An Advisory Group should be appointed from the renal community to provide guidance. These actions should be part of the integral charge to the HCFA Health Data Policy Committee to develop an overall comprehensive data strategy for HCFA.

Recommendation #2: PREVENTION

1) Initiation of a primary prevention program focused on the education and behavior modification of the hypertensive and toxic nephropathy population; 2) expansion of basic and clinical research into the physiological processes which occur in renal disease in order to enhance the possibilities of increasing the number of preventable conditions which now lead to ESRD.

Recommended Action: This task should be delegated with lead responsibility to the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, which should coordinate with the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung, and Blood Institute within the National Institutes of Health of the Public Health Service (PHS). These activities include basic and clinical research into hypertension and kidney disease as well as the ongoing PHS hypertension program which deals with public education and prevention.

Recommendation #3: RESEARCH AND EVALUATION

Development of a cohesive clinical and program research plan directed to the goals of reducing the incidence of ESRD, of improving the treatment of ESRD and of developing program steps to improve the economy and efficiency of ESRD care.

Recommended Action: The clinical and biomedical aspects of this research plan should be delegated with lead responsibility to the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases which should coordinate with the National Institute of Allergy and Infectious Diseases and the National Heart, Lung and Blood Institute within the National Institutes of Health of the Public Health Service. HCFA should be charged with undertaking program evaluations and research studies in the areas of gaps in program information. These two actions should produce a coordinated basic and clinical/biomedical program research plan to reduce the incidence of ESRD, to improve the treatment of ESRD, and to develop program steps to improve the economy and efficiency of ESRD care.

Recommendation #4: TRANSPLANTATION, REUSE, AND REHABILITATION

TRANSPLANTATION:

To develop a research plan to improve the results of kidney transplantation, to develop a prototype public education format to encourage organ donation, and to reestablish a transplant information data base.

Recommended Action: The task of reestablishing a national transplant registry should be charged to the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases within the National Institutes of Health of the Public Health Service, to work in conjunction with the American Society of Transplant Surgeons. This DHHS component should also be charged with the task of undertaking a study to examine current surgical removal techniques for kidneys, methods for kidney preservation, methods of kidney donor and recipient transportation, transplantation surgery techniques, immuno-suppressive therapy; and reasons for kidney wastage.

DIALYZER REUSE:

To undertake a prospective clinical trial to determine the efficiency and safety of reuse and to identify potential long-term effects of prolonged reuse.

Recommended Action: The recommended action here is to assign the Food and Drug Administration the responsibility to undertake a prospective clinical trial employing discrete hemodialyzer sterilizing and disinfecting procedures. The study would report its findings from which generalizations could be drawn not only regarding efficiency and safety but the long-term effects of prolonged reuse of hemodialyzers. The final report would include a specific set of recommendations for standards that could be incorporated into regulatory authority to govern hemodialyzer reuse.

REHABILITATION:

HCFA is presently studying (through Battelle Memorial Institute) the impact of alternative types of therapy on quality of life, the quality of care and the cost of care for the ESRD patient, and the tradeoffs between quality of life and quality care offered by one type of treatment versus another. The study will also describe the extent of disability among renal patients in three treatment modalities. This study will not be completed until January 1983. HCFA has also convened a National Rehabilitation Task Force which has recommended that barriers to vocational rehabilitation for ESRD patients be eliminated, information for ESRD patients on employment and related benefits be improved; provide incentives to employers through vocational rehabilitation to reduce barriers to hiring ESRD patients.

Recommended Action: This task should include a charge to the Department of Education to clarify vocational rehabilitation opportunity for ESRD patients. Also necessary is a charge to the Social Security Administration to review laws and/or regulations that set up "automatic" nature of disability entitlement by virtue of ESRD diagnosis and to explore feasibility of statutory change to allow continuation of partial disability cash benefits to ESRD patients who work part time. Another recommended action is the establishment of a

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
[illegible] DIV.
4402 NORTH 7TH STREET
PHOENIX, AZ 85014-4198

May 23, 1983

David A. Ogden, M.D., F.A.C.P.
Chief, Renal Section
Department of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724

[redacted]

ATTACHMENT L

Dear Dr. Ogden:

This letter is written in response to your request for our current views on dialyzer disinfection. It is our understanding that you will consider these views as suggestions in the current review of the National Kidney Foundation Interim Standards for Reuse of Hemodialyzers.

During the past year, we have been involved in a field investigation and subsequent laboratory studies associated with an outbreak of nontuberculous mycobacteria (NTM) bacteremias in hemodialysis patients traced to contaminated reprocessed dialyzers. It is possible that some of these dialyzers reached patients in a contaminated state as a result of failure to add any or sufficient formaldehyde to the blood and/or dialysate compartments, since verification of formaldehyde at the patient station was not routinely practiced. However, we did isolate viable microorganisms from samples of formaldehyde solutions taken from blood compartments of several dialyzers up to 5 days after reprocessing. These resistant organisms included some slow-growing gram-negative bacteria as well as NTM. Similar types of organisms were isolated from various points throughout the RO water treatment, storage and distribution systems, suggesting that the water used both for rinsing dialyzers and preparing 2% formaldehyde was the source of the contaminants found in dialyzers and the pathogens isolated from infected patients.

As you know from our previous communications, we have expressed concern about the possibility of this type of outbreak occurring because our work with some waterborne strains of NTM had demonstrated a high level of resistance to both chlorine and formaldehyde. To reduce the risk of contaminating dialyzers with these organisms during reprocessing we had suggested that the formaldehyde solution used to fill clean dialyzers always be passed through a 0.22-µm filter. Further, we stated that water used to clean and rinse dialyzers contain less than 200 viable bacteria per ml as measured by the AAMI guidelines. It had been our experience that water meeting this microbiologic criterion would not contain sufficiently high levels of formaldehyde-resistant organisms to contaminate dialyzers with a bioburden capable of resisting a 15 hour exposure to 2% formaldehyde solution. However, results of studies conducted during the past year have shown that these assumptions may not always be valid.

We now have evidence that in water systems where low levels of a residual disinfectant, such as chloramine, are maintained, the normally dominant water bacteria are suppressed and populations of resistant organisms become predominant. For instance, assays of RO water from the center in which the outbreak occurred showed levels of NTM as high as 1200 per ml in the absence of any other types of bacteria. Because NTM and other germicide-resistant organisms may require several days to exhibit growth on culture media, the AAMI assay procedure which calls for only 48 hours of incubation would not have detected microorganisms in the sample referred to above. Therefore, it appears that even though water used to rinse dialyzers meets the AAMI criterion it may contain a sufficient number of germicide-resistant organisms to result in contamination of reprocessed dialyzers.

Using pure populations of formaldehyde-resistant NTM, we conducted a series of laboratory tests to determine the levels of contamination that might be expected in dialyzers rinsed with water containing various levels of these organisms and subsequently filled and stored for 24 hours with 2% formaldehyde. We found that the number of viable bacteria that could be recovered from processed dialyzers was directly proportional to the concentration in the rinse water. The lowest level of bacteria in rinse water which still resulted in the recovery of viable organisms from dialyzers was 38 per ml. From this we concluded that rinse water should be free of germicide-resistant bacteria if 2% formaldehyde solution is to be used as the disinfectant.

In modifying our suggestions of 1 year ago, it appeared that we could offer 2 options:

1. Utilize aseptic techniques throughout dialyzer processing procedures and use only sterile rinse water and sterile 2% formaldehyde solution. This would eliminate the introduction of microorganisms into dialyzers and the formaldehyde solution would serve only as an added measure of safety. However, the adoption of this option would require strict quality control involving monitoring of handling procedures as well as routine microbiologic testing of rinse water. These requirements appear to be costly and cumbersome for both manual and automated processing systems.

2. Adopt the use of 4% formaldehyde solution as the disinfectant and require a minimum exposure time of 24 hours. Our laboratory results show that this time-concentration combination will effect more than a 6 log reduction in the most resistant waterborne populations of NTM. Since NTM do not appear capable of reaching concentrations greater than 10^5 per ml in most natural water environments, a margin of safety would appear to exist for this disinfection procedure. A consequence of adopting this option would be an increase in the time required to remove the formaldehyde from the dialyzer at the patient station.

We believe that option no. 2 would be the easist to implement and reliably practice. The routine use of existing sensitive (1-2 ppm) tests for residual formaldehyde should prevent any increase of patient exposure. We also would emphasize the need for reliably achieving a 4% level of formaldehyde in po the blood and dialysate compartments of every dialyzer. We have found levels of formaldehyde in manually processed dialyzers to vary because of the difference in the total volume of formaldehyde solution passed through the dialyzer in the process of filling. Our tests indicate that a minimum of 3 blood compartment or dialysate compartment volumes of solution must be exhausted before the level of formaldehyde in the dialyzer reaches the same level as that found in the supply tank. Finally, we would emphasize the need to confirm the presence of disinfectant in each processed dialyzer.

We hope these suggestions will be helpful and urge you to contact our laboratory if questions arise.

Sincerely yours,

Norman J. Petersen

Martin S. Favero, Ph.D.
Assistant Director for
Laboratory Science and
Chief, Dialysis and Applied
Microbiology Branch

Norman J. Petersen

Norman J. Petersen
Assistant Chief
Dialysis and Applied
Microbiology Branch

MSF/NJP:bwg

REUSE COMMITTEE MINUTES

Members

new # on

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Kathy Shanahan	HFK-117
Evelyn Gordon	HFX-4
Robert Skufca	HFX-200
Fernando Villarroel	HFK-420
Norman Welford	HFK-420
Nancy Leonard	HFX-18
Norb Neib	HF~~Z-460~~ -73
Nancy Clemente	HF~~Z-460~~ - 74
Sally Hedrick	HFX-76
Charlotte Silverman	HFX-10

Date: November 9, 1983

Discussions

1. The Georgetown University Conference on Hemodialysis was briefly discussed by the Chairperson, who will be attending an organizational meeting on November 10. At our next meeting, He will brief the Committee on the planning logistics for the conference, i.e., speakers, statement of objectives, finances, etc.

2. The Committee discussed extensively Glenn Rahmoeller's October 24, 1983 request for review of the Center's policy on exportation of used pacemakers. Robert Forst, an attorney in the Office of Standards and Regulations, stated his agreement with the position of the Division of Compliance Operations (Lee Mathews' memorandum of November 9, 1983). He also pointed out that if the Center wanted to collect supplemental data on the reuse of pacemakers, that could be accomplished under the premarket approval or investigational device exemption processes but that it would be difficult under the 510(k) process. It was Mr. Forst's opinion that the provisions of §515(e) apply to reused pacemakers, and that the persons manufacturing and relabeling the pacemaker are required to have an approved PMA or IDE. From a scientific point of view, the Committee unanimously agreed that reuse of pacemakers is acceptable if they can be adequately reprocessed, i.e., resterilized, refurbished, etc. The Committee, however, would like to caution that there are also ethical and political issues, and that the whole question of reuse must eventually be addressed. It was recommended that the Division of Cardiovascular Devices assume the "lead" role in the scientific and technical issues of these devices.

3. The revised Reuse Inventory Form was distributed and a few minor changes made. Larry Kobren and Linda Suydam will meet with Mr. Britain to discuss its distribution to the classification panels. Larry will draft a cover memorandum and distribute it to the Committee for comment.

4. Dr. Villarroel requested that the Committee review a draft Memorandum of Need (MON) for guidelines in the reuse of hemodialyzers. The Committee also discussed how the results of the MON shoul be used. It was suggested by Larry Kobren that perhaps the Association for the Advancement of Medical

Instrumentation (AAMI) could establish a committee to develop the guidelines if FDA provided, as a result of the MON, the necessary risks and hazards data.

5. Dr. Villarroel also requested that the Committee draft a response to a letter (August 15, 1983) from Dr. Kay of the Montreal General Hospital on studying the reuse of hemodialyzers.

Action Items

1. Review MON for guidelines on the reuse of hemodialyzers (Section 3 in particular) by Thanksgiving and submit comments to Larry Kobren (all members).

2. Draft response to Canadian letter concerning the reuse of hemodialyzers (Kobren).

3. Brief Committee on results of the organizational meeting for the Georgetown University Conference on Hemodialysis (Kobren).

4. Draft cover memorandum for the Inventory Form (Kobren) after meeting with Mr. Britain (Kobren and Suydam).

Next Meeting:

OPEN

cc: Robert Forst HFX-460
DONNA LENAHAN HFX-18
John A. Bittenbender HFK-116

prepared by LKOBREN:lbp REUSE-FORM in TDW. 11/22/83

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

November 30, 1983

Medical Director
Dialysis Services

Dear Doctor:

Since 1982, the Food and Drug Administration (FDA) has been monitoring reports concerning severe hypersensitivity reactions with new dialyzers (also called first-use syndrome) that occur in end-stage renal disease patients. These anaphylactic-like reactions occur in patients within the first few minutes of a dialysis treatment and require that the dialysis procedure be stopped immediately. Manifestations include nausea, malaise, weakness, a sensation of burning or heat throughout the body, profuse perspiration, respiratory distress and in some instances hypotension and cardiopulmonary arrest. Although the frequency of occurrence of these severe reactions is low (3 to 4 reactions per 100,000 dialyzers sold in the U.S. during 1982), they may be life threatening and require that resuscitative measures be initiated.

Experts at the "Symposium on Hypersensitivity in Hemodialysis" held in Louisville, Kentucky, on July 21 and 22, 1983, discussed possible causes of this reaction. One potential cause is traces of residual material from the manufacturing process in the dialyzer blood path. The discussants believed that water is the most effective flushing agent known for removing any residues, and emphasized the importance that the user strictly adhere to the manufacturer's rinsing and priming recommendations, as this procedure serves not only to remove air but also to reduce any trace amounts of residual material that might be left from the manufacturing process. They also noted that residual material might not be completely removed by the rinsing procedure performed by manufacturers, who cannot use water for rinsing if the dialyzer is to be sold dry. (The proceedings of this workshop will be published in Artificial Organs.)

FDA has examined case reports and found that about sixty percent of the severe hypersensitivity reactions reported in 1982 occurred with dialyzers that were rinsed using procedures other than those recommended by the manufacturer.

In view of the above, it would seem reasonable to assume that improved rinsing of the dialyzer by the user should minimize the risk of a patient having a hypersensitivity reaction. Therefore, FDA recommends:

1) Strict adherence to the dialyzer rinsing and priming procedure given in the labeling of the device, as a minimum.

2) That all personnel concerned with dialyzer preparation be informed that if appropriate rinsing and priming procedures are not followed, susceptible patients may be at greater risk of having hypersensitivity reactions.

3) That all hypersensitivity reactions be fully and promptly reported to the dialyzer manufacturer.

If you have any questions, please contact Dr. Fernando Villarroel, Director, Division of Gastroenterology-Urology and General Use Devices at (301) 427-7750.

Sincerely,

Marlene E. Haffner, M.D., F.A.C.P.
Acting Director
Office of Health Affairs (HFK-200)
National Center for Devices
and Radiological Health

AAMI REUSE GUIDELINE DRAFTING COMMITTEE

MINUTES OF THE 5 DECEMBER 1983 MEETING

American Society of Nephrology Convention
The Washington Hilton
Washington, D.C.

I. CALL TO ORDER

Dr. Ronald Easterling, chairman of the Drafting Committee, called the meeting to order at 7 p.m. Judith Veale, AAMI staff, served as recording secretary. The following persons attended the inaugural meeting of the Drafting Committee:

Lee Bland, representing the Centers for Disease Control as an alternate for Martin Favero, Ph.D.
Dennis Cotter, representing the Georgetown University Institute for Health Policy Analysis as an alternate for Seymour Perry, M.D.
Margaret Diener, representing the National Association of Patients on Hemodialysis and Transplantation as an alternate for A. Peter Lundin, M.D.
James Dugan, representing the Health Industry Manufacturers Association
Ronald Easterling, M.D., representing the Association for the Advancement of Medical Instrumentation
R. Wayne Fields, Ph.D., representing B-D Drake Willock, Inc.
Lee Fischbach, representing Renal Systems, Inc.
Michael Fisher, representing the National Kidney Foundation
Lawrence Kobren, representing the National Center for Devices and Radiological Health, U.S. Food and Drug Administration
Curtis Lynch, M.D., representing the Sporicidin Company
Thomas K. Sawyer, M.D., representing the Northwest Kidney Center, Seattle
Betty Whipple, R.N., representing the American Association of Nephrology Nurses and Technicians

Elizabeth Bridgman, of the American National Standards Institute, also attended the meeting in her capacity as the designated successor, effective 2 January 1984, to Judith Veale as AAMI's Manager for Technical Development.

II. OPENING REMARKS

Dr. Easterling noted that the meeting had been convened to initiate work on a national consensus guideline for reuse of hemodialyzers. He indicated that this project was an outgrowth of AAMI's May 1983 technology assessment conference on reuse of disposables, at which meeting there had been expressed a strong consensus feeling that there was a need for consensus guidelines on reuse.

The group reviewed the response to date from organizations and individual experts that had been invited to participate in the AAMI committee.

(SECRETARY'S NOTE: In addition to the representatives listed above in the attendance roster, Dr. William Dornette and Ms. Bonnie L. Eckart, CCSM, who were unable to attend the meeting, had been designated as the representatives of the American College of Legal Medicine and the International Association of Hospital Central Service Management, respectively. Also, the Association of Operating Room Nurses, though unable to send a representative to the 5 December meeting, had responded favorably to the invitation to participate; until an official representative is designated, Ms. Rosemary Roth will be participating on behalf of AORN. Subsequent to the meeting, it was learned that Dr. Frank Gotch, who had been invited to serve as an individual expert, would be unable to participate.)

The meeting participants also reviewed related activities being undertaken by other organizations. It was noted that the Georgetown University's Institute for Health Policy Analysis was planning a 29-30 March 1984 meeting (at the Sheraton Washington in Washington, D.C.) as a follow-up to the 1982 reuse meeting convened by Dr. Sadler and the AAMI conference on reuse held in May 1983. Mr. Cotter indicated that this meeting would address the reuse of a number of types of medical products, not just hemodialyzers. He went on to report that 9 questions were being formulated for discussion at the conference. A conference report several weeks after the meeting would summarize those areas where agreement was reached among the participants as well as areas of disagreement. The general format of the conference, Mr. Cotter noted, was as follows: During the morning of the first day, there would be a session on general principles of reuse. During the afternoon, there would be specific sessions on reuse of cardiac catheters, intensive care devices, nephrology devices, respiratory therapy devices, and "miscellaneous" devices which are commonly reused but which do not fit conveniently into the preceding four categories. On the second day, the chairpersons of each of these break-out sessions would report the findings and recommendations of each group. Mr. Cotter noted that the American Hospital Association, the Food and Drug Administration, and the National Institutes of Health would be participating in the Georgetown project. (See Attachment A for a more detailed description of the planned Georgetown conference.)

Mr. Kobren reported that an ad hoc group of HCFA, FDA, and NIH representatives had been established, with the objective of conducting a retrospective long-term study on the potential morbidity and mortality associated with reuse. Mr. Kobren noted that there were several data bases that could serve as sources of information, including HCFA ESRD data. Mr. Kobren also made reference to a survey to be distributed to 40,000 health care professionals to obtain further data on reuse.

There was general discussion of the status of guidelines which were under development by various organizations and which could serve as "point-of-departure" documents for the AAMI committee's work. These included the National Kidney Foundation's draft "Revised Standards for Reuse of Hemodialyzers," which Mr. Fisher indicated could be distributed to the AAMI committee (see Attachment B for January 984 draft); the state of California's proposed regulations for hemodialyzer reuse (Attachment C); the second draft of the Michigan ESRD Network Coordinating Council's "Standards for Dialyzer Reuse" (Attachment D); and Renal Systems Inc.'s

"Dialyzer Reprocessing Guidelines" (Attachment E). It was noted that the states of New Mexico and Colorado had also developed regulations on reuse.

Dr. Easterling indicated that none of these activities obviated the need for national consensus guidelines on reuse, and he noted that the reason AAMI had been identified as an appropriate forum for the work was that AAMI has had established, recognized process for establishing consensus as well as existing committees with expertise in hemodialysis and in sterilization processing. He went on to advise the group that in AAMI's consensus-development program "standards" were conventionally directed to medical device manufacturers, whereas "guidelines" were typically directed to medical device users. In the present case, Dr. Easterling observed, the initial objective was to develop a consensus guideline aimed at device users, although the parallel question of the need for a standard for reprocessing machines will likely be taken up in the future.

III. SCOPE AND TIMETABLE

The meeting participants reviewed a draft "Statement of Need, Objectives, and Scope" which had been prepared by AAMI staff as a basis of discussion for the AAMI committee (Attachment F). Dr. Easterling noted that it was important that an AAMI guideline on reuse of hemodialyzers provide functional criteria, rather than design- or process-limiting criteria, in order to provide maximum flexibility for health care professionals establishing their individual programs.

Mr. Dugan asked why the Reuse Guideline Drafting Committee had not been chartered under the auspices of the AAMI Renal Disease and Detoxification Committee. Dr. Easterling and Ms. Veale replied that as initially contemplated by the AAMI management, the scope of the project was broader than the reuse of hemodialyzers. Ms. Veale commented that the development of a guideline for the reuse of hemodialyzers had been identified as the initial project, since there was wide interest in this area and since there was more data available for hemodialyzer reuse than for the reuse of other types of disposables. She noted, though, that one objective of the meeting was to obtain further input from interested parties on the exact dimensions of the activity.

> (SECRETARY'S NOTE: Subsequent to the 5 December meeting, the AAMI Standards Board had further discussion of the organization and scope of the project. It was agreed that while there were some general principles in common between reuse of hemodialyzers and reuse of other disposable medical products, it would be appropriate from an organizational standpoint to charter the "Reuse Guideline Drafting Committee" as a Subcommittee under the AAMI Renal Disease and Detoxification Committee. The subject of reuse of other medical products would be deferred to the AAMI Sterilization Standards Committee for consideration, with a view to ascertaining the interest in chartering a separate Subcommittee or Working Group under this committee.)

Dr. Sawyer asked whether home reuse of hemodialyzers was to be included within the scope of the guideline. Dr. Easterling replied that the same principles would apply and that home reuse could be covered either as a specific section in the guideline or via qualifications of the general provisions. Dr. Sawyer indicated that home reuse must be addressed carefully, since there were special considerations involved here. Dr. Easterling observed that the guideline was intended to be directed to physicians, as it was assumed that reuse, whether at home or in a health care facility, would be carried out under the supervision of a physician. Dr. Sawyer suggested that this be made explicit in the text of the guideline, and there was general agreement that this would be appropriate. There was also general agreement that, for planning purposes, the committee would attempt to address home reuse not as a separate subject but, rather, in the context of the general provisions.

There was considerable discussion of whether "aesthetics" should be addressed in the guideline, since this subject had not been identified in the draft outline for the guideline. Dr. Sawyer commented that aesthetics was a difficult characteristic to define, since it did not lend itself to quantification. Several participants observed, on the other hand, that it would be beneficial to at least discuss aesthetics in the guideline, even if quantifiable criteria could not be developed, since many patients are concerned about the appearance of a reused hemodialyzer. Consensus was ultimately reached that, at least for the time being, aesthetics would be considered to be within the scope of the guideline. This was done by adding a section on "inspection" in the section on reprocessing.

Mr. Dugan noted that there were significant differences in configuration among conventional hemodialyzers (i.e., flat-plate, hollow-fiber, coil) and asked whether the intent was to cover all three types in the guideline, given that the most commonly reused hemodialyzer is the hollow-fiber type. There was general agreement that, for planning purposes, all types of hemodialyzers would be addressed.

In concluding this discussion, Dr. Easterling commented that the general initial goal of the committee should be the development of a draft guideline by the spring of 1984, which could then be further refined and made available as a basis for discussion at a fall 1984 AAMI conference on reuse.

IV. OUTLINE OF THE GUIDELINE

The group then turned to a specific review of the proposed outline offered in the draft "Statement of Need, Objectives, and Scope" for the guideline on reuse of hemodialyzers. There was general agreement that the major remaining objective of the planning meeting was to refine this outline and make work assignments.

Upon considerable discussion, the following revised outline was created. After each section, the committee member assigned the development of a first draft of the section is identified.

I. Equipment Selection (LeRoy Fischbach)

II. Definitions and Reference Documents (Lawrence Kobren)

III. Physical Plant Considerations (James Dugan)
Environmental Safety (James Dugan)
Storage of Reprocessed Hemodialyzers (James Dugan)

IV. Personnel Qualifications and Training (Michael Fisher)

V. Patient Considerations--Medical Issues, Informed Consent (Margaret Diener, Peter Lundin, M.D.)

VI. Reprocessing
  a. Terminating Dialysis (Betty Whipple)
  b. Rinsing/Cleaning (Betty Whipple)
  c. Performance and Leak Testing (Ronald Easterling, M.D.)
  d. Inspection (Curtis Lynch, M.D.)
  e. Disinfection (Lee Bland)

VII. Preparation for Dialysis and Testing for Toxic Residues (Ronald Easterling, M.D.)

VIII. Patient Identification and Hemodialyzer Labeling/Storage (Michael Fisher)

IX. Patient Monitoring and Documentation (Betty Whipple)

X. Quality Assurance and Quality Control (Wayne Fields, Ph.D.)

There was general agreement with the objective that each participant would submit his/her work assignment, the first draft of the appropriate section, by 15 January 1984. The work assignments would then be compiled into a first draft of the guideline by Dr. Easterling. Mr. Kobren commented that it would be helpful to future progress if the first draft of the guideline were as comprehensive as possible, since it was always easier to revise and delete in the development process than to create new information de novo. To facilitate the work, AAMI staff agreed to distribute to all participants copies of the existing guidelines discussed at the meeting (see Attachments B-E).

> (SECRETARY'S NOTE: In light of the revisions to the guideline reported above, the second paragraph of the proposed scope appearing in Attachment F should also be revised, to read as follows:
>
> "This guideline is directed to all individuals and institutions who reprocess hemodialyzers either manually or by an automated method. Subjects included within the scope of this guideline are: equipment selection; patient considerations (medical, informed consent); personnel requirements and training; physical plant and environmental safety considerations; reprocessing including guidelines for termination of dialysis, rinsing, cleaning, testing and disinfection of the reprocessed hemodialyzer; preparation for dialysis; patient identification; patient monitoring and documentation and quality control and assurance.")

V. TIME AND PLACE OF NEXT MEETING

Appropriate sites/dates for the next meeting of the committee were identified as the March 1984 Georgetown conference on reuse and the May 1984 convention of the American Society for Artificial Internal Organs (ASAIO). It was agreed that the exact particulars of the next meeting would depend on the progress made with work assignments.

VI. ADJOURNMENT

Dr. Easterling thanked meeting attendees for their interest and participation and adjourned the meeting at approximately 10 p.m.

McCue,
FYI; please
return for my
file.
Thanks
Tom

thanks
Jim

REUSE COMMITTEE MINUTES

Members	
Jim Chantler	HFZ-323
Kathy Shanahan	HFZ-323
Evelyn Gordon	HFZ-70
Robert Skufca	HFZ-70
Fernando Villarroel	HFZ-420
Norman Welford	HFZ-420
Nancy Leonard	HFZ-30
Norb Heib	HFZ-83
Nancy Clements ✓	HFZ-84
Sally Hedrick	HFZ-250
Charlotte Silverman	HFZ-104

Visitors	
Robert Forst	HFZ-84

Date: January 25, 1984

Discussions

1. Larry Kobren reported on a meeting held for all PMS chairpersons. The importance of public speaking (in particular, briefings) was emphasized. Arrangements have been made with Toastmasters for special training sessions for all PMS chairpersons and members, if they want to attend.

2. Minutes of the last meeting were—reviewed and "Action Items" updated.

   o The Canadian letter requesting FDA funding for a hemodialyzer reuse study was determined to be an unsolicited proposal and therefore denied, because the United States government does not normally fund foreign research.

   o The MON for developing a guideline for reuse of hemodialyzers (Dr. Villarroel) is no longer needed, since the Association for the Avancement of Medical Instrumentation (AAMI) has agreed to develop a guideline.

3. Mr. Kobren reported on the organizational meeting of the Georgetown University Resue Conference. Reuse of hemodialyzers will be included in the Conference, but it will not be the main topic. Arrangements are being made for members of the reuse Committee to attend gratis or at a reduced fee. Mr. Villforth will present a speech on regulatory concerns, and Committee members were asked to solicit possible topics from their organizational units.

4. Mr. Kobren and Ms. Suydam met with Mr. Britain regarding the Reuse Inventory Form. The form has been simplified to one page and will be used by the Classification Panel Executive Secretaries. Hopefully, inormation gathered by the form will be availabe for the Georgetown University Reuse Conference.

5. AAMI held a working group meeting (attended by Mr. Kobren) to begin developing a guideline for the reuse of hemodialyzers. The guideline

will include sections on plant specifications, personnel selection/training, patient considerations, medical considerations, reprocessing, preparation for dialysis, references, and a glossary. Mike Miller of AAMI is meeting with NCDRH Staff to explore possible FDA financial support for the development of the guidelines.

6. A lengthy discussion was held by the Committee on the issue of reuse of pacemakers (see minutes of November 9, 1983 meeting). The committee was divided in its opinion on whether the Center should consider reprocessed pacemakers as subject to the requirement of 515, i.e., requiring a PMA submission. The Chairperson was scheduled to meet with the Center Director and other organizational units on this important policy issued.

Action Items

- o Possible topics to be used by Mr. Villforth in his speech at the Georgetown University Reuse Conference. Submit to Mr. Kobren by Monday, February 6.

Next Meeting:

2:00 p.m., Conference Room T-400, February 15 (Wednesday)

cc: Robert Forst HFZ-84

**Association
for the
Advancement
of Medical
Instrumentation**

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Arlington, Virginia 22209
703/525-4890

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Memorial Hospital System, Houston

W. A. Tacker, Jr., M.D., Ph.D.
Purdue University

AAMI

TO: Members and Alternates of the
AAMI Hemodialyzer Reuse Subcommittee

FROM: Elizabeth A. Bridgman
Manager for Technical Development

DATE: 25 April 1984

SUBJECT: Notes of 28 March 1984 meeting

Enclosed for your information are my notes of the 28 March 1984 subcommittee meeting, as well as copies of the documents distributed at that meeting. With the AAMI Annual Meeting intervening between subcommittee meetings, I regret that it has not been possible to prepare formal minutes.

I look forward to seeing you at the next subcommittee meeting on 4 May.

EAB

cc: Information List (w/encl)

AAMI Hemodialyzer Reuse Subcommittee
28 March 1984
Sheraton Washington Hotel

TRANSCRIPTION OF NOTES BY E.A. BRIDGMAN

1. Meeting called to order 7:10 p.m. by EAB in absence of chairman. EAB distributed copies of written comments, received, from J.T. Boag and S. Burrows-Hudson. (See Attachment 1 for attendance; Attachments 2 and 3 for comments.)

2. Consideration of Boag comments:

(1) J. Dugan pointed out that we did try to take other existing standards into account. L. Kobren commented that he would prefer a more structured format for the AAMI document, similar to the format of the California standard. EAB pointed out that AAMI recommended practices (as opposed to standards) can and often do incorporate elements of rationale into the main body of the document rather than placing them in a separate appendix.

(2) B. Whipple noted that in some respects tubing sets are already included. J. Dugan recalled T. Sawyer's comment at last meeting that tubing reuse was not as widespread, and noted that scope for document was needed. Scope could state that document is limited to reuse of hemodialyzers, and excludes products such as blood lines, fluid infusion lines, transducers, etc. Scope could note that these items will be covered in a future document. At present there is far less experience with blood lines. (After chairman's arrival, proposed scope was distributed, and it was noted that we could get back to this.)

(3) Note that 7.1.2 and 6.5.4 leave open the method of test. The method suggested in this comment could be offered as one possible method, e.g. in an appendix. (On arrival, chairman pointed out that his outline suggests an appendix on test methodologies)

(4) There was general disagreement with this comment. The differences are so great that the two types of systems must be treated separately.

(5) Complex procedures may be beyond the capability of some centers.J. Dugan pointed out that California regulation says you must do control testing. After that, periodic testing. Other approach is what manufacturers do -- sample from each batch. This could be very costly. Once your procedure is set up, you're set -- follow GMP, for example. You just have to continue to follow the tested and validated procedure. Sections 1.3.1.1 and 1.3.2.1 already address Boag's comment.

(6) J. Dugan disagreed with comment, pointing out that some dialyzers can be ruined in the rinsing process. There was general agreement that the test should be retained, that it is easy with hollow fiber units, which are those most commonly reused. After arrival of chairman, there was considerable additional discussion. Experience is that reused units have one third the leaks of first use. Chairman suggested that if you have a method that you know does not increase the leak rate, then this is not necessary. A log should be maintained and reviewed periodically.

(7) F. Gotch suggested there was no point in discussing this point in the absence of data.

3. Format of reuse guideline

Chairman distributed proposed outline, foreword, introduction, and scope. Suggested that glossary be moved either to beginning or end of document. (Note: AAMI practice is to place glossary at end.) Noted that some of Lundin's language had been moved to introduction; Lundin agreed.

4. Page-by-page review of draft guideline

1.1.1 Delete second sentence.

1.2.1.1 Must this be done if no bacteria growth is found? Ogden proposed change -- should address issue of getting disinfectant out.
1.2.1.2 Pyrogen test is unreliable. How about instead of this, recording before and after temperatures. Marilyn Case agreed to provide data. Then we can go to CDC (?) and tell them we have a problem.

1.3.1 Re Burrows- Hudson comment, note that water quality mentioned here is that required to make the machine work.

1.3.2 Delete reference to human error.

1.3.2.1 Move to QC section. Do we want to specify arbitrary intervals?
1.4 Move to QC section.
1.6.1 Re Burrows-Hudson comment, frequency should be checked with OSHA, as should formaldehyde levels for 1.6.

Glossary:

Dialyzer: delete "hemodialysis filter" . Use definition from hemodialyzer standar
Hazard: ... to patient or staff safety.
ppm: first "p" lower case
Reuse Number: change to "Use Number"

3.1 Change heading to "Area for Reprocessing Hemodialyzers"

3. Chairman noted that nowhere do we address record-keeping procedure, i.e. what records should be kept and where. Need for this to be covered should be kept in mind.

3.1.3 Needs to be changed. Question whether clinic should have to follow same requirements as manufacturer. FDA position is that clinical use is different from manufacturing. View expressed that making this so stringent will turn people off to entire guideline.

3.1.4 Delete -- covered later.

3.2 It was suggested that some points should be stressed relative to the process, others relative to the processor. In general, area for reprocessing should be equivalent to area where dialysis is performed (treatment area); we should specify what this is. Test of operational adequacy is absence of problems. Need specifics regarding conditions, including specific test methods, as appropriate, in appendix.

3.2.2 Non-shedding gowns unnecessary.

3.5 Change heading to "Supplies"

3.6 Belongs elsewhere.

3.7.4 Delete "quarantine".

3.7.5 Belongs elsewhere.

4. NANT will prepare a contribution.

4.2.1 Chairman proposed additions.

5. Chairman suggest beginning this section with contraindications, e.g. elevated enzymes. Lundin suggest beginning with medical indications, e.g. patients with first use syndrome. Chairman suggest main points are informed consent and patients' rights. Various comments: Much of this section is philosophical -- does not belong in recommended practice. This document should cover how patients' concerns are addressed, not factors like trust and the doctor-patient relationship. Does cost-saving reference belong here? Could some of this go into an appendix? California seems to be taking the position that legally the patient cannot refuse reuse -- this is a matter of the practice of medicine. Legal aspects of issue should be checked out with lawyer. This section could be in a section on implementation of reuse program or management of reuse program. EAB will discuss legal aspects and AAMI concerns with M. Miller.

6.1.2 Change to: "Dialysate ports are to be capped with clean port caps."

6.2.1 Should be repositioned as final step.

6.2.2 Delaying reprocessing may increase clotting. If delayed over a specific length of time, should refrigerate.

6.2.3 Define appropriate saline solution.

6.4.4 Delete parenthetical statement.

6.5.1 It could be noted that the concentration (4%) is unsettled, opinions vary. Minimum of 24 hours' contact time also questioned. It makes more sense (in one view) to monitor for mycobacteria than to require 4% formaldehyde.
6.5.2 Filtering should come before final cleaning.

6.5.4 Three month intervals questioned.

7.1.3 ...dialysate flow, if appropriate, which has been documented

7.1.4 Gotch will prepare statement of rationale for 5 ppm.

7.1.7.1 Question whether notation should be made on label.

8.1 ...Patients with similar last names should be identified, e.g. by color coding,to alert staff.

9.3(2)Add: "(in absence of other causes for fever)".

5. Future meeting plans

The next discussion of the reuse guideline will take place in conjunction with the meeting of the AAMI Renal Disease and Detoxification Committee immediately following the ASAIO conference on May 4th. Another meeting may be held in conjunction with the ISO working group meeting in Los Angeles on 9-10 June. The chairman confirmed that a national consensus conference on hemodialyzer reuse will be sponsored by AAMI in the fall. (Exact dates: 5-6 November, Los Angeles)

ATTACHMENT 1

AAMI Hemodialyzer Reuse Subcommittee
Meeting of 28 March 1984 - Washington, DC

ATTENDANCE

Elizabeth Bridgman, AAMI
Ronald Easterling, M.D., Hurley Medical Center (Subcommittee Chairman)
Lawrence Kobren, CDRH/FDA
Jim Dugan, CD Medical Inc. (HIMA)
Ben J. Lipps, Seratronics
Marilyn Case, Associates of Cape Cod, Inc.
Marilyn Urps,National Association of Nephrology Technologists
Lee Fischbach, Renal Systems, Inc.
Kristi Duffy, APIC
Rhonda Bell, Culligan
Peter Lundin, M.D., NAPHT
David A. Ogden, M.D., National Kidney Foundation
Albert E. Jarvis, Ph.D., CD Medical Inc. (AAMI)
Luke Schmieder, Mesa Medical Inc.
Elizabeth Whipple, R.N. AANNT
Frank Gotch, M.D. Ralph K. Davies Medical Center
Norman Deane, M.D., Manhattan Kidney Center (RPA)

Service Facility Regulation
  Administration
614 H Street, N. W.
Washington, D. C. 20001

APR 12 1984

Mr. Robert J. Taylor
Associate Regional Administrator
Division of Health, Standards & Quality
Region III
P.O. Box 7760
Philadelphia, Pennsylvania 19101

Dear Mr. Taylor:

Recently a complaint was received in our office regarding the reuse of blood lines in an End Stage Dialysis Center. Enclosed find a copy of the complaint investigation.

Since we have never had blood lines reused before, we called Lee Bland at the Center for Disease Control (CDC) for information regarding blood line reuse.

Mr. Bland stated that CDC does not have a reuse blood line policy but recommends that hospital guidelines for central service department would be appropriate in reuse processing areas. For example:

(a) The facility should develop written procedure and training guidelines.

(b) Reuse blood lines should not be used for hepatitis patients.

(b) That formaldehyde residue should be below 5 ppm.(National Kidney Foundation).

He also stated they should have:

1. Decontamination Room

2. Sterilizing and or clean storage room

3. Handwashing facilities in decontamination room.
4. Adequate ventilation.
5. Storage racks for blood lines should be a minimum of 5 feet off the ground.
6. Number of times line used should be limited.

We need to know HCFA's policy on re-using blood lines. If HCFA decides to allow re-use we will need written guidelines on how to monitor its use.

Please advise us on this issue as we understand other BMA's in the District are contemplating adopting re-use of blood lines.

Sincerely,

Frances A. Bowie
Acting Administrator

DCRA/SFRA/JMcPherson/es/4/11/84

✓SFRA chron file
Director's chron file
Dictator 's copy
Facility file

REUSE COMMITTEE MINUTES

Members

Jim Chantler	HFZ-323
Kathy Shanahan	HFZ-323
Evelyn Gordon	HFZ-70
Robert Skufca	HFZ-70
Fernando Villarroel	HFZ-420
Norman Welford	HFZ-420
Jim Norman	HFZ-30
Norb Heib	HFZ-83
Nancy Clements	HFZ-84
Sally Hedrick	HFZ-250
Charlotte Silverman	HFZ-104

Date: April 12, 1984

Discussions

1. Mr. Kobren discussed the change in the PHS Committee functions: the committee will no longer develop objectives - they have been replaced by issues, which the PHS committees believe will define activities in which the Center needs involvement. Mandatory activities (which the Center is required to do) and discretionery activities which are deemed worthy of being worked on but which will not need followup will be defined by the Committees.

2. The Reuse Committee members discussed the Reuse Conference. The consensus of the committee members was that it was a productive meeting; but that few if any real problems with reuse were defined; and that hospitals seemed to be doing a good job with the reprocessing. Some persons who reuse devices stated that it would be helpful to them if the manufacturers would provide guidance in the labeling with regard to the use of certain cleaning materials, sterilizations procedures, or high level disinfection procedures.

3. Mr. Kobren read a draft of a letter he had prepared for Mr. Villforth's signature addressed to General Council. The letter requests their opinion and interpretation of 21CFR 801.4 which requires manufacturers who are aware that their device is being used for purposes other than for which it was intended to address that use in their labeling.

4. The next meeting of the AAMI committee for the development of a Recommended Practice for the Reuse of Hemodialyzers will meet on May 4, 1984, in conjuction with the ASAIO meeting. After the preparation of the next draft of the document, copies will be given to the members of this committee for review. It is important that the various offices within the Center with intrest in this matter get their input into the document at an early stage in its development. Mr. Kobren will collocate the comments and send them to the AAMI chairman.

5. Mrs. Hedrick said she would begin compiling a bibliography on reuse of

medical devices. Whether each member wants to maintain the bibliography will be decided later.

6. The 1981 the Bureau of Medical Devices compliance policy regarding reuse was discussed. More pressures are being exerted for reuse now and are likely to increase even more in the future. We believe the policy should be reexamined in light of these new pressures and we should consider whether revision or modification of our policy is necessary.

7. The Committee decided it might be helpful to develop a Center Guideline on the various issues of reuse, such as sterility, disinfection, cleaning,and materials. The guideline would give help and direction to the various offices in the Center. Each member was asked to query his office for ideas on what should be included in such a guideline.

Action Items

1. Members will obtain input from their offices regarding a Center reuse guideline.

2. Members will obtain input with regard to possible changes to the Center compliance policy.

Next Meeting

May 10,1984 Room T-400 1:30-3:00

Drafted:LKobren:jts:4/23/84 called REUSE-MIN in LNK

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

APR 19 1984

Mr. J. Kevin Rooney
Attorney at Law
15 Rocky Hill Road
Upper Saddle River, New Jersey 07458

Dear Mr. Rooney:

This is in further response to your letter of March 9, 1984, to Mr. Thomas Scarlett, General Counsel for the Food and Drug Administration (FDA), concerning reuse of hemodialysis devices.

Hospitals that utilize raw materials in the manufacture of drugs are regulated by FDA as drug manufacturers and are required to register as such.

This is not the case with hospitals involved with the use of hemodialysis devices which are recleaned and reused. In the case of the reuse of dialyzers a patient-doctor relationship exists. If the doctor orders the reuse of a dialyzer on his patients, we have considered this to be in the realm of the practice of medicine which is controlled by other governmental bodies, more specifically, State authorities.

I trust this answers your inquiry.

Sincerely yours,

for Walter E. Gundaker, Director
Office of Compliance
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES   Public Health Service

Centers for Disease Control
Atlanta GA 30333

April 20, 1984

Ronald E. Easterling, M.D.
1906 Penbrook Lane
Flint, Michigan 48507

Dear Ron,

Thank you for your recent letter where you requested rationale for the justification of using 4% formaldehyde for the sterilization of dialyzers that are reprocessed.

I appreciate and sympathize with the committee's concern about CDC's recommendation for using 4% formaldehyde or equivalent for the disinfection of reprocessed hemodialyzers. Obviously, much of this concern deals with the increased rinsing time required to remove residual formaldehyde. However, there is one element concerning this subject that is independent of the recommendation to use 4% formaldehyde and that is the requirement of one or more states that have a concentration of 1 ppm or less of formaldehyde which, if one adheres to 95% confidence limits, significantly increases the rinsing time, not only with 4% formaldehyde but also with 2% and the glutaraldehyde formulations as well. I believe first and foremost that efforts should be made to change that interpretation because I think that we are all in agreement that documenting that low a residual of formaldehyde routinely is not necessary.

As you know, CDC has never felt comfortable with the use of 2% formaldehyde because it was not truly part of a sterilization process nor hardly qualified even as a high-level disinfection process. Further, when it became evident that the nontuberculous mycobacteria might be a more realistic challenge group of microorganisms to consider rather than the gram-negative water bacteria when considering dialyzer disinfection and reprocessing, it became clear that 2% is inadequate. Unfortunately, there are no extant data in the literature that describe the efficacy of concentrations of formaldehyde less than 4% (i.e., 3%) or with the glutaraldehyde formulations or other disinfectants.

Consequently, there appears to be two options that can be considered. A dialysis center could ensure the absence of mycobacteria either by demonstrating by culturing techniques that they are not present or by eliminating them and other organisms (for example, by filter sterilization) and subsequently continue to use 2% formaldehyde. However, there are two major problems with this approach. The culturing techniques are complicated and are not standardized at the present time. In my opinion, most dialysis centers would not have the capability or even access to the capability to adequately ensure the absence of nontuberculous mycobacteria by culturing techniques. Further, should the guideline suggest absence of mycobacteria in a specified volume of water tested (i.e., 100 ml) or no more than a specific number per volume of water? Currently, there are no answers to this question. Second, filtering water and simultaneously using aseptic techniques as a means of assuring an absence of nontuberculous mycobacteria does not appear to be a realistic approach and, if attempted, could prove to be time consuming and expensive.

This then leaves the second option which is basically to use 4% formaldehyde without testing directly for nontuberculous mycobacteria and assuming, if they were present, that this level of germicide for at least 24 hours' contact time would safely ensure their absence from a reprocessed dialyzer.

Of course, what is needed is additional information on lower concentrations of formaldehyde, as well as the effectiveness of other types of disinfectants on this group of bacteria.

As you know, we are in the midst of a study designed to determine the frequency with which mycobacteria are found in treated water of 150 randomly selected dialysis centers in the United States. To date, we have completed assays on 39 such centers and have detected mycobacteria in water in 35 of them. Consequently, I think the problem of mycobacterial contamination is much more widespread than we ever anticipated several years ago and certainly needs to be considered by the committee. Obviously, these figures may change upon the completion of this study, and I hope to have an updated set of data by the time of the meeting on May 4.

Sincerely yours,

Martin S. Favero, Ph.D.
Chief
Nosocomial Infections Laboratory Branch
Hospital Infections Program 1/B341

MINUTES

AAMI HEMODIALYZER REUSE SUBCOMMITTEE

4 May 1984
Washington, DC

1. Opening of the meeting. The meeting was called to order at 1:30 p.m. by the cochairmen, Dr. Ronald Easterling and Dr. Albert Jarvis. Elizabeth Bridgman of AAMI staff served as recording secretary.

Committee and Subcommittee Members/Alternates Present

James Boag, Colorado Medical
James Dugan, CD Medical, Inc.
Norman Deane, M.D., Manhattan Kidney Center
Ronald E. Easterling, M.D., Hurley Medical Center (cochairman)
Martin Favero, Ph.D., Centers for Disease Control
LeRoy Fischbach, Renal Systems, Inc.
Jerry D.Fisher, Travenol Laboratories
Michael J. Fisher, National Kidney Foundation
Lois Foxen, St. Joseph Hospital Renal Center
Robert Galonsky, SUNY Downstate Medical Center
Frank Gotch, M.D., Franklin Hospital
Albert E. Jarvis, Ph.D., CD Medical, Inc. (cochairman)
Prakash Keshaviah, Ph.D., Hennepin County Medical Center
Lawrence Kobren, FDA/Center for Devices and Radiological Health
Nathan W. Levin, M.D., Henry Ford Hospital
Douglas Luehmann, Hennepin County Medical Center
A. Peter Lundin, M.D., NAPHT
Curtis L. Lynch, M.D., The Sporicidin Co.
Joseph H. Miller, M.D., Wadsworth VA Medical Center
Vincent Pizziconi, Ph.D., Arizona State University
Marie H. Reid, FDA/Center for Devices and Radiological Health
John H. Sadler, M.D., University of Maryland
Thomas K. Sawyer, M.D., Northwest Kidney Center
Donald Stephens, Drake Willock
James Stewardson, Cobe Laboratories
Fernando Villarroel, Ph.D., FDA/Center for Devices and Radiological Health
Elizabeth Whipple, R.N., AANNT

Guests Present

Elizabeth A. Bridgman, AAMI Staff
Barbara L. Brown, Becton Dickinson Co.
Ellen Craven, CD Medical
Paul Duke, Mesa Medical Inc.
Gary Mills, Drake Willock
Roberta Thorpe, Erika, Inc.

Dr. Easterling stated that, in view of the limited time available for this meeting, it would not be possible to discuss in detail all sections of the draft recommended practice for reuse of hemodialyzers. He suggested that the subcommittee consider at this meeting several important issues on which consensus had not yet been reached, and reserve a detailed review of the document for a future meeting. Comments from Marilyn Case, Ph.D. and from APIC, as well as a paper on the *Limulus* Amebocyte Lysate (LAL) test from Dr. Case (Attachment 1 to these minutes), were distributed to those present.

2. Notes of previous meeting. Dr. Easterling explained that formal minutes of the 28 March 1984 subcommittee meeting had not been prepared, but that informal notes had been circulated with Ms. Bridgman's memorandum of 25 April. No comments were offered, and the meeting notes were accepted as written.

3. Format of recommended practice for reuse of hemodialyzers. Dr. Easterling reviewed the new format of the recommended practice, pointing out that the original plan of interspersing rationale with provisions had made the body of the document too cumbersome. Consequently, the rationale had been placed in a separate appendix, similar to the approach used with AAMI standards. In response to a question from Mr. Kobren regarding the inclusion of minimum reprocessing technique, Dr. Easterling suggested that this might appear in the yet to be drafted Appendix E on test methodologies.

4. Discussion of specific provisions of the recommended practice

(Secretary's Note: Following the meeting, Dr. Villarroell submitted comments on several points which were not discussed in session. These comments are identified in the following report.)

Introduction: Need for This AAMI Recommended Practice. Dr. Villarroel offered two comments on the fifth paragraph that were not considered at the meeting due to lack of time. He questioned the validity of the following sentence: "This reaction is aggravated by for-profit dialysis centers and by the position of some physicians that hemodialyzer reuse is a necessary condition for treatment in the facility for which they are responsible." He also did not agree with the statement, "The issue is not whether economies are necessary in the provision of dialysis care or even as much whether multiple usage of disposibles is a valid method of achieving such economy, but rather does delivery of quality medical care remain the first priority of physicians?".

1.0 Scope. Dr. Villarroel suggested changing lines 10 and 11 to read, "... of a device labeled for single use only (unless the manufacturer labels it for multiple use)." There was not time to consider this comment.

2.4 Complaint Investigation Record. Dr. Villarroel suggested changing "alleged problems" to "alleged common problems." There was not time to consider this comment.

3.2.1 Curriculum. NANT recommended expansion and revision of the items listed in this section. Based on the suggestions of NANT (Attachment 2) and review of this communication (Attachment 3) that were received after the meeting, the following revisions have been made.

(1) the facility's specific reprocessing procedure including a rationale for each step;

(2) basics of medical documentation;

(3) the facility's specific equipment for reprocessing hemodialyzers and, if appropriate, dialysis systems and components;

(4) microbiology as related to aseptic technique, collection and handling of samples and personnel safety;

(5) (renumbered -- formerly (4));

(6) (renumbered -- formerly (5));

(7) (renumbered -- formerly (6));

(8) (renumbered -- formerly (7));

(9) (renumbered -- formerly (8));

(10) emergency procedures;

(11) (renumbered -- formerly (9));

(12) other topics as appropriate if the person performing reprocessing has a broader scope of duties.

3.2.3 Documentation. Based on the suggestions of NANT, the last sentence has been changed to read, "Successful completion of training should be certified by the medical director of the facility and recorded in the person's personnel file along with verification of receiving the instruction by the trainee."

4.1.1 Indications. Dr. Lundin objected to subsection (1) on the grounds that these reactions are largely due to cuprophane membranes and other membranes could be used. Dr. Easterling replied that in his opinion, specifying the membrane is unrealistic, but he agreed to add a statement to the rationale addressing this issue. Accordingly, the following paragraph has been added to A4.1: "The indication of the 'first use syndrome,' e.g., 4.1.1(1), is questioned by some because these reactions are largely the result of a certain type of membrane and other membranes are available. The committee did not agree with recommending specific membranes because this is beyond the scope of the recommended practice."

4.1.2 Contraindications. Since there is no proven risk to patients arising from reuse in the presence of hepatitis B surface antigen positivity or unexplained abnormal liver function tests consistent with viral hepatitis, the subcommittee agreed to modify subsections (1) and (2) of this section to read as follows (new wording underlined):

(1) hepatitis B surface antigen positivity (unless appropriate precautions are taken to protect staff);

(2) unexplained abnormal liver function tests consistent with viral hepatitis (unless appropriate precautions are taken to protect staff);

4.2 Informed Consent. The subcommittee considered a letter from AAMI Executive Director Michael Miller which expressed concern about the inclusion of recommendations regarding informed consent in the recommended practice (see Attachment 4). Dr. Gotch reported that there had been no developments relative to this issue in California, where it appears that informed consent will remain a requirement in the state regulation on hemodialyzer reuse. Dr. Jarvis agreed with Mr. Miller that informed consent was probably not an appropriate subject to be addressed in an AAMI recommended practice. It was pointed out that attorneys who had been consulted on the issue felt that no separate informed consent is necessary for reuse, since informed consent is already secured for dialysis. Following this discussion, the subcommittee agreed to delete the specific provisions of the recommended practice dealing with informed consent (subsections (1) to (6) of 4.2). The first paragraph of 4.2 and all of 4.3 will be retained.

The rationale has been changed to reflect these revisions, by modifying the first three sentences of A4.2 to read as follows: "Initially, suggested elements of informed consent were included in section 4.2. Subsequently the committee decided, after legal counsel, that this is not appropriate for an AAMI recommended practice. The committee considered the following arguments about this issue. Those who feel that specific informed consent for use of reprocessed hemodialyzers is required maintain that greater participation in the therapeutic process need not impair the physician's ability to deliver quality care." In addition, the last sentence of A4.0 as it appeared in the April 1984 revision has been deleted.

5.1.2 Testing Water Quality. It was agreed to delete the drafting note and to modify the first sentence to read, "Product water must be tested for the degree of bacterial contamination to ensure that the requirements of section 9.2.2 are met." (Secretary's Note: The rationale for these changes is given in the minutes for section 9.2.2.)

5.2.2 Reprocessing Systems/Validation Testing. Ms. Craven questioned whether monthly validation of performance and safety of reprocessing systems was frequent enough. Dr. Easterling pointed out that this validation testing is intended to encompass the entire process, including clearance and ultrafiltration rate; frequent testing could present a problem for home patients. During the discussion which followed, it was suggested that process control procedures should be performed at least monthly, while less rigorous quality control procedures can be performed weekly. There was general agreement to change 5.2.2 to specify weekly validation testing at first.

6.2 Reprocessing Area. Dr. Jarvis expressed the view that the first sentence of 6.2 was unsatisfactory, and asked whether the physicians on the subcommittee were comfortable with it. The subcommittee agreed that more specific recommendations regarding the ventilation and other characteristics of the reprocessing area should be provided. Dr. Sawyer was asked to make available to the subcommittee the specifications for his center's reprocessing area.

9.1.1 and 9.2.1 Dr. Villarroel questioned the option of air rinsing. He pointed out that air is very difficult to get rid of in some cases and recommended that an air rinse not be mentioned at all. There was not time to consider this issue.

9.2.2 The subcommittee discussed the 1 ng/ml limit on pyrogenic material in rinsing water for used dialyzers. It was recalled that concern was expressed at the previous meeting regarding the difficulty of the LAL test for measuring this material. The information submitted by Dr. Case (Attachment 1), who was not able to attend the meeting, indicated that reliable tests for this amount of bacterial lipopolysaccharide are readily available. Several of those present also thought that the measurement of 1 ng/ml can be achieved clinically. They felt that the concern expressed previously was generated by experience with testing for much lower levels of pyrogens. Others questioned whether the rinsing water should be required to meet the 1 ng/ml limit for pyrogenic material; they suggested it be required only for water used as disinfectant diluent, and optional for rinsing water. It was pointed out that some systems use the same water for rinsing and diluting the sterilant or disinfectant. Concern was also expressed regarding the impact of the requirement on home dialysis. Following this discussion, it was agreed to limit specification of a maximum bacterial polysaccharide concentration in the rinse water to the case where the rinse water is also used to dilute the sterilant or disinfectant. (Secretary's Note: The following has been added to the rationale, section A9.2.2, to reflect these considerations:

> "Initially, a maximum level of bacterial lipopolysaccharide of 1 ng/ml was proposed for the rinse water. Questions about the availability of a suitable test for this level of pyrogen contamination were found to result either from misunderstandings about the sensitivity required or from experience with certain tests that are unreliable. Further, the possibility that some Limulus Lysate reactive materials are not pyrogenic was considered irrelevant because patient safety requires ensuring a low level of bacterial lipopolysaccharide in the water. Nevertheless, it was decided to delete the requirement for pyrogen testing of the rinsing water unless it is used to dilute the sterilant or disinfectant since the pyrogen level of the sterilant or disinfectant has been shown to be the key factor in pyrogenic reactions during dialysis (Peterson et al, 1981).")

9.3 Performance Measurements. Ms. Craven asked whether reused blood tubing should be subject to spallation testing. Dr. Easterling noted that tubing is included within the scope of the recommended practice if it is reprocessed as a unit with the dialyzer. Mr. Boag was asked to draft a section on validation testing for blood tubing when reused in this manner.

9.4 Sterilization/Disinfection. Dr. Favero, referring to his letter of 20 April 1984 to Dr. Easterling (Attachment 5), discussed the Centers for Disease Control recommendation that reused dialyzers be disinfected with 4% formaldehyde or the equivalent. He noted that in the past it had been assumed that the principal bioburden in reprocessing dialyzers would be gram-negative water bacteria; as time passed, however, it was discovered that another organism, nontuberculous mycobacteria, might pose a more realistic challenge. As noted in Attachment 5, a CDC survey in progress showed that the incidence of mycobacterial contamination is far more common than previously thought. Furthermore, studies have shown that 2% formaldehyde is not sufficient for some populations, even with exposures of 96 hours. What is missing in the literature, Dr. Favero said, is any study of 3% formaldehyde; or data on the effectiveness against mycobacteria of other widely used disinfectants, which may prove to be more effective than either 2% or 4% formaldehyde. He added that the alternative approach of filter sterilization appeared to be impractical, based on the experience of intravenous equipment manufacturers, and might well be more expensive than disinfection with 4% formaldehyde.

During the discussion which followed, it was pointed out that no information is available on the effect of radiation on mycobacteria. Mr. Boag stated that the National Kidney Foundation decision to recommend 4% formaldehyde was based on legal considerations. Dr. Lundin questioned which approach was best for patients. Dr. Easterling noted that many centers had for years reused dialyzers which were disinfected with less than 2% formaldehyde, without encountering any problems. While it is true that some of the diseases caused by mycobacteria are very difficult to detect, he added, these and other concerns are already addressed in the rationale of the recommended practice. Routine monitoring of the water used in dialysis centers is not the answer, since the assays are too difficult and in any case they are performed "after the fact." Dr. Pizziconi reported that his experience with monitoring of water supplies led to the conclusion that the water needs treatment; he suggested that a requirement to this effect be added to the recommended practice.

Based on this discussion, the subcommittee decided to retain the 4% formaldehyde requirement, but to state in the rationale that no conclusions can be drawn at this time about the adequacy of 3% formaldehyde. The drafting note in 9.4.1.1 will be deleted, and additional discussion will be included in the rationale. Dr. Pizziconi was asked to draft a provision regarding water treatment.

9.4.1.3 Procedure. Dr. Villarroel questioned the necessity for the flushing of the dialyzer with three volumes of sterilant or disinfectant. There was not time to consider this matter.

10.3 Testing for the Presence of Sterilant or Disinfectant. Mr. Michael Fisher reported that his center uses process controls, for example, checking holding tanks, rather than testing for the presence of sterilant or disinfectant in the stored dialyzer as recommended in 10.3. He suggested that the procedure of 10.3 could give a false sense of security. Mr. Fisher was asked to draft wording which would permit the alternative procedure which he described.

10.4.1 Testing for Residual Sterilant or Disinfectant. The subcommittee discussed the 5 ppm maximum recommended concentration of residual formaldehyde. Dr. Sawyer suggested that the rationale for this provision should be the same as that for trace elements. Dr. Jarvis proposed that the rationale be expanded to reference Dr. Gotch's study when published. Mr. Boag pointed out that it may take longer for a reprocessing machine to rinse out than for a dialyzer to rinse out, so the level of residuals in machines should be checked as well.

13.0 Glossary

Clearance, Closed-Loop Method. Dr. Villarroel commented that the definition of "b" is incorrect because regression analyses do not have slopes (curves do). He also questioned the term "patient reservoir" in the definition of V_o. There was not time to consider these comments.

Fiber Bundle Volume. Dr. Villarroel suggested that this definition should include the volume of the headers. Time did not permit discussion of this point.

Label. Dr. Villarroel pointed out that this definition is used by the FDA for the term "labeling." There was not time to consider this issue.

5. Plans for further development of the recommended practice. It was recalled that AAMI planned to hold a national consensus development conference on the reuse guideline on 5-6 November 1984 in Los Angeles. There was general agreement that at least one full day session of the subcommittee was needed before the end of the summer to permit a more complete review of the draft recommended practice prior to the conference. It was hoped that the subcommittee could achieve consensus on the draft (or close to it) by the time of the conference. The selection of a convenient date and location for the next meeting was left to the cochairmen and staff. (Secretary's Note: The next meeting has been scheduled for 22 August 1984 in Chicago, provided a sufficient number of members are able to attend.)

6. Adjournment. The cochairmen adjourned the subcommittee meeting at 3:20 p.m. so that the meeting of the Renal Disease and Detoxification Committee could convene as scheduled.

REUSE COMMITTEE MINUTES

Members

Jim Chantler
Kathy Shanahan
Evelyn Gordon
Robert Skufca
Fernando Villarroel
Norman Welford
Nancy Leonard
Norb Heib
Nancy Clements
Sally Hedrick
Charlotte Silverman

Guests

Blix Winston, OMS

Date: May 10, 1984

Discussions

1. Reuse Issues for Annual Planning Process. Blix Winston, OMS, discussed the modified role of the PMS Committees in the annual planning plan, i.e., the PMS Committees will concentrate on issue identification and the Offices will be responsible for "on going" projects. In the case of Cross Cutting Committees such as the Reuse Committee, issues should be identified and submitted to the appropriate PMS Committee. If the issue involves more than one PMS Committee, then a meeting should be scheduled with OMS (Linda Suydam) for presentation to the Center management. June 5 is the deadline for getting the issue to OMS.

2. Copies of Mr. Villforth's recent speech at the Georgetown University Reuse Conference distributed and members were asked for their reviews by May 14, since it will soon be published in the meeting proceeding.

3. Legal Opinion on Reuse Requested. Copies of a memorandum from Mr. Villforth to General Counsel requesting a legal opinion on the applicability of §801.4 were distributed to the committee. Office of Standards and Regulations is requested to review §801.4 and the draft reuse policy and give a legal opinion of both.

The subcommittee felt that this section was unnecessary, in view of the information provided in 3.2.3, and decided to delete it.

3.2.3 Documentation

The final sentence of this section was revised to read as follows (new words underlined): "Successful completion of training should be certified by the medical director or his or her designated representative ..."

4. Patient Considerations

4.1 Medical Issues

4.1.1 Indications

There was general agreement that, while the cost savings associated with reuse is important, the emphasis on it in 4.1.1(2) was inappropriate, and this subsection was accordingly changed to read as follows: "(2) the quality of and/or access to dialysis is maintained or enhanced as the result of the cost savings arising from reprocessing hemodialyzers."

4.1.2 Contraindications

It was agreed to delete the parenthetical references to protecting staff in the presence of hepatitis B surface antigen positivity and abnormal liver function tests consistent with hepatitis, but to add a comment to this effect in the rationale. It was noted that there is some experience with multiple use of dialyzers for patients with hepatitis and that in these units the reprocessing procedure is done in isolation areas separate from reprocessing of dialyzers for patients without hepatitis. The subcommittee also decided to add the presence of AIDS as a contraindication.

4.2 Informed Consent

It was agreed that the second and third sentences of this section more properly belonged in the rationale.

4.3 Physician/Patient Relationship

The suggestion was made that the issue of the physician/patient relationship had no place in a document on reprocessing, but it was pointed out that the issues raised in this section were ones that a practitioner would have to face when initiating reuse, and that guidance should be given. The section will be reworded as follows: "Patients have expressed concerns about the quality of medical care they receive when using reprocessed hemodialyzers. Assurances about these matters are best served by a frank discussion concerning reprocessing procedures." It was also suggested that the rationale make reference to the concept of a social contract, as described at a recent conference by social scientist Richard Rettig. (Secretary's note: The following rationale was added to A4.3: "The committee decided to include this point of information in view of the concerns of some patients about the adequacy and safety of reprocessing procedures and the possibility that cost savings from multiple use of hemodialyzers might be used to contribute to the economic benefit of others rather than to improve the quality of care. The

4. The planned ECRI meeting on reuse has been postponed until fall.

5. A copy of Glenn Rahmoeller's response to the Mayo Clinic request to export reused pacemakers was distributed to Committee members. Since this issue had been previously considered by the Committee, there was no discussion of the letter.

6. AAMI Guideline for Reuse of Hemodialysis. Submit Office reviews to Chairperson as soon as possible.

7. A letter of appreciation from the GU Institute for Health Policy Analysis was received by the Chairperson. Copies were distributed to the Committee and the possibility of conducting a reuse survey was discussed. Because the Office of Management and Budget (OMB) restrictions on conducting research surveys, possible funding by FDA is doubtful (Dr. Silverman represents the Center on matters relating to surveys and she discussed the OMB restrictions).

Action Items

- Reuse Policy - Get Office reviews and return comments to Chairperson by May 31.

- Reuse Issues for Planning Process - Any possible reuse issue should be sent to the Chairperson by May 31.

- Review of AAMI Guideline for Reuse of Hemodialysis - Get Office review as soon as possible and submit to Chairperson.

Next Meeting

June 7 (Thursday), 1:30 p.m., Conference Room T-400

DEPARTMENT OF HEALTH & HUMAN SERVICES **REGION III**

Memorandum

Date JUL 03 1984

From Acting Chief
Survey and Certification Review Branch, Region III

Subject Request a review and policy disposition regarding the reuse of arterial and venous blood tubing sets for renal dialysis

To Patricia Harfst, Director
Division of Institutional and Ambulatory Services

We received the attached complaint investigation report from the District of Columbia state survey agency involving the reuse of blood lines in an End-Stage Dialysis Center.

The state agency telephoned the Centers for Disease Control (CDC) to obtain guidance. CDC does not have a reuse blood line policy and recommended guidelines for central service that would be appropriate in reuse processing procedures.

We feel that the health and safety issues involving reuse of the dialyzer are similar in this situation. There should be a national policy disposition regarding the reuse of blood tubing in order to ensure the protection of the health and safety of patients.

In addition to the above complaint investigation, the state agency informed us of another recent complaint. In this situation the renal dialysis facility had no available guidelines for reuse of blood tubing.

The manufacturer's label clearly indicates, "for single use only" (See Attached)

We expect that the above will become a national concern thus, we would appreciate a review and policy issuance that can distributed to the state survey agencies.

We are currently delaying the recertification of two end-stage renal dialysis facilities pending your review and because of the potential significant impact on the health and safety of patients.

If any additional information is required, please do not hesitate to contact me.

Claudette V. Campbell
Claudette V. Campbell

Attachments

5/2/84

Food and Drug Administration

DRAFT

Director, Center for Devices and Radiological Health, HFZ-1

Request for Legal Opinion of the Applicability of Section 21 CFR 801.4

General Counsel, GCF-1

The Institute for Health Policy Analysis, Georgetown University Medical Center recently sponsored an International Conference on the "Reuse of Disposable Medical Devices in the 1980's". Interest in the reuse of medical devices has become intense due to the pressure to contain medical costs by government and third-party payers. It is believed that considerable savings can be achieved by hospitals who reuse certain medical devices.

The conference, attended by over 500 persons from the health care community including physicians, hospital administrators, nurses, technicians, supply purchasers, consumers, regulators, and manufacturers explored this topic, as well as the legal, ethical, medical, scientific and technical considerations associated with the practice of reuse.

In my remarks to the conference I discussed the Center's views on the reuse issue, both from the regulatory and public health points of view. I explained to the conference that the medical device amendments gives us the authority only to regulate the manufacturers of devices and not the user of these devices. I pointed out that the responsibility for reuse of a device labeled "for single use only," as outlined in our Compliance Policy Guideline 7124.16 dated July 1, 1981, falls directly on the user of the device. In addition, the guideline makes it clear that the reprocesser must demonstrate that (1) the device is adequately cleaned and sterilized; (2) its physical characteristics are not affected; and (3) it remains safe and effective.

Many at the conference understood our regulatory position and appeared to be willing to assume the responsibility for reuse. However, they were concerned that they did not have enough information about devices to allow them to effectively reprocess them. Little has been done to assure the safety and effectiveness of devices which have been reused (hemodialyzers excepted) or to document procedures for quality control.

From a public health standpoint, it is vital that this information be made available. Since the manufacturers should know the limitations of their devices better then anyone else, voluntary labeling by them with regard to these limitations would be useful. From the manufacturer's point of view however, this may not be possible because of the presumed liability associated with this type of labeling.

Because of the pressures generated, primarily by government, to hold down costs, the apparent increase in reuse by hospitals to save money, and the liability considerations of the manufacturers which prevent them from giving instructions for proper reprocessing procedures, the patient is ultimately placed at greater risk.

I believe that the FDA has a responsibility to address this issue directly. In my remarks to the reuse conference, I raised the possibility that in certain special circumstances it may be possible to invoke 21 CFR 801.4 which requires that manufacturers, who are aware that their device is being used for purposes other than for which it was intended (reuse for example) be required to address that use in their labeling.

A specific example of this is in the area of hemodialyzers. It is common knowledge in the hemodialysis community that over 51 percent of hemodialysis patients are being treated with reused devices and over 90 percent of patients using hollow fiber dialyzers are being treated with their reused hollow fiber dialyzer. Reuse of hollow fiber dialyzers has apparently become standard medical practice.

Therefore, I would like your help to conduct a formal review on the question regarding the applicability of using 21 CFR 801.4 to require manufacturers of devices which are known to be reused to provide adequate instructions regarding reuse procedures in their labeling. Specifically:

1. Can section 801.4 be used to require a manufacturer to provide information on the proper cleaning, disinfection, and testing procedures to follow for the reuse of his product even though he intends to sell it for one-time use only?

2. What evidence would be necessary to show that the manufacturer "knows or has knowledge of facts" that his device is being reused?

3. If we invoke this section of the law, what procedures should be followed?

I would appreciate your consideration of this issue at your earliest convenience. My staff and I would be happy to meet with you to discuss this matter in more detail.

John C. Villforth

cc:
W. Gundaker, HFZ-300
R. Britain, HFZ-400
P. White, HFZ-80
W. Dierksheide, HFZ-800
W. Johnson, HFZ-100
Reuse Committee

HFZ-240:LKobren:jts:4/10/84 called REVIEW8014 IN LNK
reviewed:JArcarese
JCVillforth

1876

COLORADO DEPARTMENT OF HEALTH

Richard D. Lamm
Governor

Thomas M. Vernon, M.D.
Executive Director

TO : ALL HEALTH FACILITIES LICENSED BY THE HEALTH FACILITIES REGULATION DIVISION OF THE COLORADO DEPARTMENT OF HEALTH

FROM : HEALTH FACILITIES REGULATION DIVISION

SUBJECT: SINGLE USE DISPOSABLE MEDICAL DEVICES

Several changes have been made to Section 7, Chapter II, Colorado Department of Health Standards for Hospitals and Health Care Facilities regarding Single Use Disposable Medical Devices. The changes primarily effect the reuse of dialyzers and quality control for dialyzer regeneration.

Please check your old copy of Section 7 against the new Section 7 which is enclosed, so that you will be aware of the modifications in effect as of 08/30/84, and adopted by the Colorado Board of Health on 07/18/84.

4210 EAST 11TH AVENUE DENVER,COLORADO 80220 PHONE (303) 320-8333

CHAPTER II

7

SINGLE USE DISPOSABLE MEDICAL DEVICES

7.1 Applicability. This section is applicable to all health facilities licensed by the Department.

7.2 Basis and Purpose. Statutory authority for adoption of these regulations is C.R.S. 1973, 25-1-107(1)(1)(I) and 25-1-108(1)(c)(I). The regualtions are proposed to control the re-use of single-use or disposable medical devices. Without such regulations, the public health safety may be jeopardized.

7.3 Definitions:

7.3.1 A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent or other similar or related article intended for use in the diagnosis of disease or in the cure, mitigation, treatment or prevention of disease." Examples are cardiac pacemakers, glass clinical thermometers, catheters, cardiac guidewires, renal dialyzers, etc.

7.3.2 A single-use or disposable medical device is one labeled as such by the manufacturer, or one in which a caution is included in the accompanying literature or catalogue recommending one time only usage.

7.3.3 Dialyzer Regeneration means the preparation for reuse of a single-use dialyzer in accordance with this Section 7 of Chapter II.

7.4 Policy Statement.

7.4.1 The re-use of medical devices labeled as single-use or disposable shall be prohibited with the following exceptions:

1. Dialyzers for the same patient.
2. Ballon-assist catheters (opening but not inserted).
3. Devices not requiring maintenance of sterility (irrigation and other patient devices).

7.4.2 Prior to re-use of any items except dialyzers list in 7.4.1 (reuse of which is subject to the provisions of 7.5, 7.6, 7.7), the facility shall submit the the Department for approval written processing procedures which shall meet the following guidelines based on F.D.A. standards:

1. The device can be adequately cleaned prior to disinfection and reuse.
2. The physical characteristics of the device material will not be adversely affected by cleaning, disinfection, or re-use.
3. The packaging material will allow effective penetration of the disinfecting agent and will prevent recontamination of the device under the storage conditions to which the devices will be subjected.
4. If disinfecting process is effective.
5. If the treated device is used parenterally, the process will not evoke pyrogenic response.
6. The device, after gas or chemical disinfection, will not contain toxic residues.

7.5 Dialyzer Regeneration.

7.5.1 Regeneration shall not be permitted on dialyzers used for hepatitis antigen positive patients.

7.5.2 Prior to individual dialyzer regeneration, each patient shall be provided by the physician with a presentation of possible complications and hazards and possible benefits of such regeneration. This shall be incorporated into the consent for dialysis form and shall become a part of the patient's dialysis record. Patients shall have access to the number of times their dialyzer has been reused.

7.5.3 No person shall be denied access to dialysis in the facility as a result of that patient's refusal to permit regeneration of his or her dialyzer. Refusal to permit regeneration shall be documented.

7.5.4 The facility shall document the qualifications of and the protocols for training personnel responsible for the regeneration process.

7.5.5 The facility shall provide training for all personnel in the protocols and procedures for regeneration at the time of employment and no less than annually.

7.5.6 The facility shall establish policies and procedures to ensure the safety of employees in regard to the use of disinfecting agents and procedures to deal with accidents and spillage of disinfectants.

7.6 Quality Control for Dialyzer Regeneration. Procedures shall be established and documented in the facility procedure manual which shall include but not be limited to:

- 7.6.1 Each dialyzer to be resued shall be indelibly and clearly labeled with the patient's name and other unique identifying information before the initial use.
- 7.6.2 At each subsequent use, the label shall be checked by two separate individuals, the dialysis staff member and the patient, if feasible.
- 7.6.3 The number of the uses shall be recorded both in a reuse record maintained for each dialyzer, and in the patient's permanent dialysis record.
- 7.6.4 Water used to formulate cleaning solution and to rinse dialyzers shall be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter (0.45 micron) which is appropriately maintained. This water shall contain less than 200 bacteria per ml, which shall be documented by bacteriologic sampling of the source water outlet in the reprocessing area monthly. Where such sampling reveals bacterial counts that periodically approach or exceed this limit, corrective measures and weekly sampling shall be accomplished. Results of such samples shall be recorded.
- 7.6.5 Disinfection shall be achieved with an effective agent, the addition of which to each dialyzer shall be documented and recorded. If formaldehyde is used as the disinfecting agent, a mimimum concentration of 2% in both the blood and dialysate compartments, and minimum exposure time of 24 hours if required.
- 7.6.6 Disinfection shall be monitored epidemiologically of all febrile reactions during dialysis with new or used dialyzers and shall be documented in the patients record.
- 7.6.7 Blood and dialysate cultures shall be done on all patients during febrile reactions. Reports of cultures shall be recorded in the dialysis record.
- 7.6.8 Documentation and recording of the addition of effective disinfectant concentrations in the dialyzer to be reused shall be done.

7.6.9 Documentation and recording of effective disinfectant removal from each dialyzer immediately prior to reapplication shall be done. Validation tests of methodologic achievement shall be made monthly.

7.6.10 Removal of any other potentially toxic substances added as any part of the reprocessing procedure shall be documented and recorded by routine testing and/or validation studies as appropriate.

7.6.11 The effectiveness of the reprocessing procedure must be documented before each subsequent use of each dialyzer.

1. For hollow fiber dialyzers, a hollow fiber bundle volume (HFBV) of not less than 80% of the initial HFBV, measured at 0±10 MM. of HG transmembrane pressure, shall be maintained.
2. For parallel plate or coil dialyzers, small molecular clearance tests shall be performed during or after each use, performance less than 90% of original capacity will not be permitted.

7.6.12 Blood leaks during use of both new and reprocessed dialyzers shall be documented and recorded. If the blood-leak rate of used dialyzers exceeds that of new dialyzers, each dialyzer must be pressure tested for possible blood compartment leak before reuse.

7.6.13 Dialyzers shall be discarded unless the following criteria are met at the time the dialyzer is to be used on the patient:

1. The dialyyer has no cracked or broken parts.
2. The dialyzer appears clear and free of dissolved or residual blood manifest by a brownish or pinkish tinge.
3. Headers are visibly free of all but small peripheral clots.

7.6.14 A clean storage space for disinfected dialyzers will be provided.

7.6.15 Where such committee exists, all quality control procedures shall be approved by the Infection Control Committee.

7.7 Dialyzer Regeneration Facilities. A separate room shall be provided.

7.7.1 Unless the room is equipped with an appropriate flushing system, the room shall be equipped with a counter and counter sink.

7.7.2 The room shall have approved hand-washing facilities and storage cabinets.

7.7.3 The room shall be separated in clean and soiled areas. Regeneration dialyzers shall be maintained only in the clean area.

7.7.4 The room shall be ventilated with fresh air at a minimum rate of six air changes per hour or locally exhausted. Air shall not be recirculated through the ventilating system except at those times when processing is not taking place. If general exhaustion of the room is selected, as opposed to local exhaustion, the site of exhaustion must be, at a maximum, six inches from floor level. (NOTE: Formeldehyde gas is heavier than air.)

7.7.5 The rooms shall be lighted to a level of 50 foot candles throughout. Light levels shall be 100 foot candles at the work surfaces.

7.7.6 Storage space shall be provided for supplies and for regenerated dialyzers proportional to the number of patients in the unit.

ADOPTED: JULY 18, 1984

EFFECTIVE: AUGUST 30, 1984

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service , SJU

Food and Drug Administration
Rockville MD 20857

AUG 1 1984

Mr. Robert Rosen, Chairman
Kidney Patients Association
8400 Bustleton Avenue, Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Rosen:

This is in response to your letter of May 31, 1984, addressed to President Reagan in which you expressed your concerns about the reuse of dialyzers. The letter was forwarded to us for response because dialyzers are devices subject to regulations issued by the Center for Devices and Radiological Health, (CDRH), Food and Drug Administration (FDA).

The reuse of dialyzers for the same patient has been practiced from the early days of dialysis and virtually all types of dialyzers have been subject to reuse. The procedures for reprocessing have been modified since those early days, paralleling the introduction of new types of dialyzers in the dialysis community, and including numerous variations in rinsing, cleaning, and disinfection/sterilization procedures. At the present time it is estimated that approximately fifty percent of dialysis patients in the United States are treated with reused dialyzers. This is an increase from an estimated 16 percent in 1980. (I might add that no dialysis centers, to our knowledge, reuse dialyzers on anyone but the same patient). As you alluded in your letter, one of the justifications for reusing dialyzers may be economic, and the recently finalized prospective reimbursement regulations may serve to further enlarge the patient population treated with reused hemodialyzers.

The economic aspects of health care are a national concern; however, you should pursue the matter with respect to cost with the Health Care Financing Administration (HCFA) which is the government agency responsible for establishing the reimbursement for the treatment of end-stage renal disease. I suggest you send your inquiry to Mr. Robert Steiner, HCFA, BERC Office of Coverage Policy, Room 401, 6325 Security Boulevard, Baltimore, Maryland 21207. Our authority relates only to the scientific and regulatory aspects of these devices and we will direct the remainder of our reply to those matters.

The increase in the number of patients treated with reused hemodialyzers is, to some extent, due to the publication of data which supports the safety and efficacy of the reuse of dialyzers. Data to this effect was published in a final report to the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases.[1] The author, Dr. Norman Deane, stated in his conclusions:

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[1] N. Deane and J.A. Bemis, "Multiple Use of Hemodialyzers. A Report to the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases", NTIA PB80215403, 5285 Port Royal Road, Springfield, Virginia 22161.

"Utilization of specified procedures (for reuse) with suitable process and quality control, will result in a reprocessed hollow fiber hemodialyzer equivalent in terms of function, cleanliness, and sterility to a new hollow fiber hemodialyzer."

All reviewers agree that the single most important determinant of the final outcome of reprocessing is the specific procedure used for reprocessing the dialyzers. The National Kidney Foundation (NKF) also recognizes that the reuse of hemodialyzers can be safe and effective if adequate reprocessing is practiced and has issued revised standards for the reuse of hemodialyzers.[2]

We agree, however, that the safety and efficacy of reuse is still a subject of some discussion. While there are some reports in the literature regarding potential adverse affects of reuse, there are many others, such as the Deane report, that indicate that dialyzer reuse is not only a safe and effective practice with minimal patient complications, but may, in fact, present fewer health complications than single use.

It should be noted that single use of dialyzers does not always ensure the absence of patient symptoms. It has been documented[3] that severe anaphylactic-like reactions related to the first use of dialyzers (first use syndrome) occasionally do occur and may be life threatening. We were concerned enough about this problem to issue an alert to physicians describing the syndrome and suggesting procedures to be followed to reduce the risk to the patient (copy enclosed).

With respect to the FDA's regulatory responsibilities with regard to reuse, you should know that the FDA regulates the manufacturer and/or distributor of the device. We do not regulate the user (i.e., the dialysis center, the physician, nursing staff, patient). Our regulatory responsibility is to insure that the device, as manufactured, is safe and effective. Our policy with respect to a person or institution who reuses a "single use" device as outlined in our Compliance Policy Guide, to which you referred in your letter, is to place the responsibility for reuse on the user who must show that the device can be adequately cleaned and sterilized; that the physical characteristics are not adversely affected; and that the device remains safe and effective for its intended use. (The suggestion, that you made in your letter, that the FDA "condemns" reuse, is not accurate). In addition, the Guide requests that any information developed regarding this practice should be referred to the CDRH for review and evaluation. Our review of any adverse reports would attempt to determine if any adverse effects resulting from this procedure was a user problem or was related to improper labeling. In case of user related problems, alerts similar to the one issued on hypersensitivity could be published.

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[2] "National Kidney Foundation Revised Standards for Reuse of Hemodialyzers," NAPHT NEWS, May 1984.

[3] "Investigation of the Risks and Hazards Associated with Hemodialysis Devices", NTIA PB80215403, 5285 Port Royal Road, Springfield, Virginia 22161.

Our regulatory efforts are also directed at the manufacturer's labeling. We review the labeling to insure that the conditions of use prescribed, recommended, or suggested in the device labeling are not misleading. In the particular case of the reuse of hemodialyzers we do not find any misleading statements by the manufacturer.

The statement "for single use only," or its equivalent, is not mandated by the FDA. Manufacturers of devices which are commercially marketed in the United States, however, are required to provide the user with either adequate directions for use or information for use to include those indications and precautions under which practitioners can use the device safely. Dialyzers must be labeled as "sterile." Manufacturers inform us that because they can not be sure that a user would follow their directions for reprocessing, they are not in a position to assume the liability which would be implicit in their labeling, guaranteeing that their device will be safe for reuse. Thus, the manufacturers say they are compelled to label the device "for single use only" or with a similar statement.

Beyond our specific regulatory authority, our Center also has a public health role regarding the safety of medical devices, stemming from the Public Health Service Act and from the labeling responsibilities implicit in the Medical Device Amendments. Under this role, the Center has initiated programs which will develop data on hemodialyzer equipment, including the reuse of dialyzers. The data will form the basis of future activities, if necessary, such as the development of educational programs which can inform both professionals and patients about the benefits and problems inherent in the process of dialysis treatment in general and reuse in particular.

In addition the CDRH is represented on the Association for the Advancement of Medical Instrumentation (AAMI) committee which is developing guidelines for the reuse of hemodialyzers. Representation from other government agencies, industry, patient organizations, and physicians are working very hard to produce a guideline that will provide guidance for reprocessing hemodialyzers with the assurance that patient safety and clinical efficacy is maintained. Perhaps your concerns should be directed to the chairperson of that committee. The meetings are open to all and input from persons with your experience is always valuable. You may get in touch with the committee by contacting Ms. Elizabeth A. Bridgman, Manager for Technical Development, AAMI, 1901 N. Fort Myer Drive, Arlington, Virginia 22209.

I hope this letter clarifies our authority and responsibilities with respect to medical device safety and effectiveness in general, and dialysis and reuse in particular. We are very sympathetic to the concerns of dialysis patients, and we are conducting our regulatory, research, and educational efforts to making sure that, to the extent possible, dialysis is a safe and effective treatment.

Sincerely yours,

/s/ John C. Villforth

John C. Villforth
Director
Center for Devices and
Radiological Health

Enclosure

230216

KIDNEY PATIENTS ASSOCIATION
8400 Bustleton Avenue
Suite 3
Philadelphia, PA 19152
(215)752-5718

May 31, 1984

President Ronald Reagan
Executive Offices
1600 Pennsylvania Avenue N W
Washington, DC 20500

President Reagan:

We are a small but rapidly expanding organization in support of correcting a great injustice which is being imposed upon many kidney dialysis patients. It is our desire that you read the contents of this letter which states our position, and help us to protect their interests as required by the Constitution of the United States.

We view re-use as a matter of Risks vs Benefits. The patients take the risk while the medical field reaps the benefits.

Medical practicioners state that, by re-using dialyzers, they are saving large amounts of money. This argument "is not persuasive for the simple reason that monies saved are not returned to the government or third party payers." It merely provides excess profits for the entrepreneur. " Health Devices, in November, 1980, advised against dialyzer re-use in any facility that could not demonstrate a specific new benefit to the patient that would offset the indeterminate added risk." To date, there still appears to be no additional benefit to the patient.

The treatment centers for patients have become an enormous business. Most establishments in this state are owned and operated by a large public corporation.

It certainly is a tedious task to convince the public that the medical profession has representatives that are more interested in monitary gains than that of the good and welfare of their patients. In our particular case, they seem to have completely disregarded the possible consequences to those placed in their care, custody and control.

In order to state our case, I have listed below the major areas of concern. Many others are also included in the Alabama report attached hereto. I, naturally, am against re-use in any manner whatso-ever. Quite frankly, it scares me to death.

Let's start with the products themselves. Dialyzers and Venous and Arterial Blood Tubing Sets are approved by the F.D.A. for single use only. This is so stated on the label in seven different lanuguages. If this product could be safely re-used, then certainly the F.D.A. would not have placed this restriction upon the users. I have enclosed a copy of the label for your perusal.

The F.D.A. regulations (attached) specifically condemn the re-use of mechanical devices of this type. Please note the specificity of the language. In an attempt to describe this phase of the problem and its possible consequences if left unchecked, we request that you accept the logic of the following situation. Your child is very sick, and you take him/her to your pediatrician. In order to cure your child, an injection of a rare toxin is mandatory. Your friendly doctor pulls out a needle, and reminds you that at the time of your last visit, this same item was used. It was his intention to re-use the needle. You were assured that it had been thoroughly cleaned with formaldehye, and although it is a deadly carcinogen, it would not affect the needle or your child. When you mentioned that the needle package stated that it was not to be re-used, you were informed that if you didn't conform to your doctor's thinking, he would not administer the injection, and your child would die. Then the doctor informed you that he was disappointed in your attitude, and that it was a pity to throw away a perfectly good needle just because the F.D.A. thought that it shouldn't be re-used. What a feeling of inadequacy and dependency. Now you can appreciate our dilemma.

The doctors argue that new dialyzers can have ill effects on patients. This is nothing but hogwash. Isn't it logical to believe that the F.D.A. and the manufacturers would be informed of each case and detailed statistics be kept? In addition, someone, somewhere would have the obligation of notifying patients of the possible effects of the devices. To our knowledge, this is not the case. There is no confirmed evidence supporting this weak argument.

Formaldehyde is a known carcinogen and mutagenic and is being used to clean the devices. They really require a sterilization process which cannot be provided. One minute particle residue, and another life is lost for the sake of a few dollars.

Different facilities use various methods of cleaning these devices. All use formaldehyde. There is no agency to double check the methodology or results of this process. How do they determine its effectiveness? I hope it isn't trial and error.

Most importantly, the cleaning process tends to render the dialyzer at least partially ineffective. There is no way to return it to its original sterility. The human factor also weighs heavily. The whole process leaves a large amount of room for negligence.

The constitution guarantees us the absolute right to reject the use of our bodies as part of an experiment. There is not enough data to support the medical facilities and their promotion of re-use. We are being coerced to act as guinea pigs in order for these Frankensteins to find an additional way to line their pockets with gold. Lives are being forfeited in the meantime.

In closing, I have attached a copy of an article from the American Medical News showing 13 deaths of patients which might have been avoided if re-use was not permitted.

It is a violation of the law to use an approved product in a matter inconsistent with its label. It is criminal in nature and is no different than any other white collar crime. We urge your support in requesting that the government take a firm stand in the enforcement of their own laws. It was obviously the intent of the F.D.A. not to permit re-use; why can't they require it? Are they so weak?

We urge you to assign this case to someone in your office who can investigate the possibilities that the practice of re-use is a violation of our civil rights, and that there may be a large conspiracy to perpetuate an equivilent of medicare fraud upon the public.

Sincerely,

KIDNEY PATIENTS ASSOCIATION

Robert D Rosen

Robert Rosen
Chairman
(14 year dialysis patient)

encl.

responsibility for this decision rests between patients and their physicians. Physicians and facilities cannot force patients to dialyze at home if they are unable or unwilling. As we pointed out in the NPRM, we expect that 30–40 percent of patients can be dialyzed at home, which means that the majority of patients will continue to receive dialysis services in a facility.

Comment: Some commenters recommended that our regulations ensure that home patients received the necessary services, arguing that facilities have a financial incentive to increase profits by not furnishing all of the services necessary for home patients. One commenter recommended that all the service requirements of the current target rate program be retained under the new composite rate.

Response: We explained above why we did not include the costs of furnishing home aides in calculating our rates. Facilities are required, under 42 CFR 405.2163, to furnish all other necessary dialysis services. This certification requirement serves the same function as the specific service requirements under the target rate agreement. Facilities are reviewed periodically to ensure that they meet all certification requirements. Patients with problems may contact their patient representative on the ESRD Network Council, or the Health Standards and Quality offices of our regional offices.

Comment: A number of commenters objected that we should not promote CAPD. They claim that is not only more expensive than home hemodialysis, but is medically unproven and possibly unsafe.

Response: We are not promoting CAPD. It has been used as an example only in so far as it is one mode of home dialysis therapy and the statute requires us to promote home dialysis. To the extent that it is more expensive than other modes of home dialysis, the incentives created by the composite rate should result in relatively greater use of the other, competing modes. As for its safety, we consulted with a panel of experts and their consensus was that, as with all modes of dialysis treatment, it was safe and effective for suitable patients. By this time, CAPD is in wide use (as of December 31, 1981 there were 4347 CAPD patients, accounting for 45.8 percent of all home patients) and the program generally covers items and services that are commensurate with generally accepted medical practice.

C. Dialyzer Reuse

Introduction.

The ESRD community is currently divided on the issue of whether it is safe to reuse dialyzers, which is one way a facility can reduce per treatment costs. In the NPRM, we explained that we were neutral on this issue; we are neither supporting nor prohibiting it in these final regulations.

Comment: Some commenters stated that, in order to increase efficiency and reduce costs, facilities should reuse dialyzers.

Response: We have no authority to require reuse. However, if a facility decides to reuse dialyzers, it will retain the savings from that practice.

Comment: Other commenters claimed that reuse is unproven and unsafe. It was also noted that some States have constraints on reuse.

Response: HCFA is neutral on reuse. Reuse is prevalent in Europe and many facilities in the United States reuse. Preliminary studies show that reuse is successful where it is done properly. Nevertheless, we do not presently require or prohibit reuse. We will continue to study dialyzer reuse, and to monitor outcomes of those facilities that reuse dialyzers, in order to determine whether we should revise the program's health and safety, as well as reimbursement, requirements with respect to dialyzer reuse.

Comment: Some commenters suggested that we set a separate payment rate for facilities that reuse dialyzers.

Response: We set composite rates based on the audits of randomly selected facilities. Twenty-five percent of the independent facilities in the audits reused dialyzers, and their costs were included in setting the rates. We cannot set separate rates for reuse because this would be impractical, since some patients in a facility may reuse, and some may not. In addition, some facilities may choose to use the savings from reuse to offset some other excessive cost in their operation. Under the prospective reimbursement system, we do not intend to adjust individual facilities' rates to their actual costs, because this removes the incentive to be efficient.

D. Prospective Rates for Self-Care Dialysis Training

Self-care dialysis training services are services that train ESRD patients to perform dialysis in the facility or in the home with little or no professional assistance, and train other individuals to assist patients in performing dialysis. Self-care training services are furnished under Medicare by dialysis facilities that are specifically approved to furnish these services. In addition, we expect many facilities that are not so approved will be able to purchase training services from approved ESRD training facilities.

Under Medicare, self-care dialysis training sessions have always been reimbursed based on a screen that is $20 more than the screen amount applicable to outpatient maintenance dialysis, except when an exception has been approved. In the absence of reliable cost data to the contrary, we will reimburse each self-dialysis and home dialysis training session by an amount equal to the facility's per treatment prospective rate exclusive of any exception amounts for outpatient maintenance dialysis plus an additional $20 per session. Facilities that have justifiable costs greater than this will be able to apply for an exception. (See above.) Based on data submitted through the new cost reports, and in applications for exceptions, we will continue to review whether this figure should be adjusted.

E. Prospective Reimbursement Rates for Peritoneal Dialysis and New Dialysis Techniques

Under Medicare, peritoneal dialysis has always been subject to the same reimbursement rules as hemodialysis sessions in the facility. As a result of medical consultations, we established an equivalence between peritoneal dialysis and hemodialysis. In the absence of cost data to the contrary, we set the reimbursement for intermittent peritoneal dialysis sessions at the same level as for hemodialysis. However, sometimes peritoneal dialysis was furnished in a single extended session of 30 hours or more in a week, in place of three separate sessions. Because the labor, overhead and supplies were more related to the total time in dialysis than the number of separate sessions, we reimbursed the extended session the same as three normal dialysis sessions in a week. Further case experience indicated the need for another intermediate reimbursement level to correspond to changing medical patterns. As a result, we provided that peritoneal dialysis sessions of 20 hours duration furnished twice per week be reimbursed at a rate equivalent to one and one-half times the payment for a hemodialysis session.

We have also set equivalencies for applying the prospective payment rates to continuous ambulatory peritoneal dialysis (CAPD) and other new techniques of dialysis. We included the costs of these treatment modes in our calculation of the weighted costs per treatment of home dialysis. CAPD is furnished on a continuous basis, not in discrete sessions; therefore we cannot pay on a per session basis. We

KIDNEY PATIENTS ASSOCIATION
8400 Bustleton Avenue
Suite 3
Philadelphia, PA 19152

August 6, 1984

Mr. John C. Villforth
Director, Center for Devices and
Radiological Health
Department of Human & Health Services
Rockville, MD 20857

Dear Mr. Villforth:

Thank you for your comprehensive reply on behalf of President Reagan. Unfortunately, since the information provided was not new to us, we could not find much that could aid the poor unfortunate patients who are forced to re-use. We understand your position in this matter, but were extremely disheartened by the admission that decisions with regards to re-use are not within the confines of your authority. We believe that you should have informed the President, and had this matter forwarded to someone in authority who had jurisdiction. We do, however, have a few comments about the letter.

You had mentioned that these re-used dialyzers are not transferred from patient to patient. The Rules and Regulations which you mention, consider these items to be adulterated unless they are sterilized. If they were indeed brought back to a sterile condition, as it was originally, then what difference would it make who received the unit? The medical practitioners claim that the protein of the patients blood remains in the dialyzer, and therefore is a benefit. Doesn't this afford an excellent opportunity to mix with the formaldehyde used in cleaning, only to be introduced into the bloodstream?

The statement regarding the National Kidney Foundation was taken out of context. It goes on to clearly state that a patient has the right to refuse the reconditioned dialyzer, and demand a new one for each hemodialysis treatment. If it is your intention to use the NKF guidelines as supportive material to prove a point which is beyond your jurisdiction, then why not take an impartial stand. I'm sure that President Reagan would settle for nothing less, since this matter effects so many people.

There must be an arm of the Federal Government that enforces your policies. The issue of re-use transcends the hemodialysis patient. It has become a way of life to many medical practitioners. If your demands are so severe upon the manufacturer, there must be some intent to protect the populace. There are no checks and balances when a facility re-uses. You have seen that physicians and drug manufacturers who financially benefit from a product or technique are reluctant to report failures. What we cannot comprehend is the loose interpretation of your own Rules and Regulations, when human lives are in the balance.

We agree that dialyzers must be sterile. The manufacturer guarantees the new device to be sterile and safe for intended use. To date, after all the years of experimentation, there still remains no adequate method of resterilizing these items. A disinfected or cleansed dialyzer should be absolutely unacceptable. Until the sterilization process had been approved by the F.D.A., then re-use of these devices should not have been permitted, and somewhere in the government, this reported violation should have resulted in appropriate action as opposed to apathetic acceptance. Data should be accumulated prior to release upon the market, not afterwards.

Not to belabor the point, but don't you think that since each institution has its own ideas as to how these devices should be cleaned, someone, somewhere should look into the methods used, and check the results. I suggest that the agency used should have the power to enforce. The incident in Baton Rouge, Louisianna, where 27 patients were contaminated by re-used dialyzers, and 13 died in 1982 should have warranted some appropriate action by an arm of the government. If this were any other item, such as a drug or food additive, it might have resulted in severe penalties, and a moretorium on the practice. The formaldehyde used, could not adequately sterilize the dialyzers. Who is responsible for the re-use of these adulterated mechanical devices? At which point will the matter become so severe that a public outcry will be demanded to rectify this intolerable condition? When issues such as this become common knowledge, heads usually roll, and politicions usually are forced to take the blame.

In closing, we must state, that all the medical organizations, and opinions in the world cannot negate the fact that under your Rules and Regulations, the re-use of a diposable medical device is not acceptable and considered to be adulterated if it cannot be resterilized. The dialyzers are not being resterilized, and therefore the perpetrators must be dealt with in accordance with the laws protecting mankind.

Very truly yours,

KIDNEY PATIENTS ASSOCIATION

Robert Rosen, Chairman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Refer to:

AUG 1 0 1984

Memorandum

984270

Date:

From: Director
Office of Coverage Policy
Bureau of Eligibility, Reimbursement and Coverage

Subject: Policy Guidance Regarding the Reuse of Disposables for Renal Dialysis (Your Memorandum Dated July 17, 1984)

To: Director
Office of Survey and Certification
Health Standards and Quality Bureau

In your memorandum you mentioned a need for interim policy guidelines to address recent complaints about reuse of disposable renal supplies, such as, dialyzers and bloodline tube sets. We are aware of complaints about reuse, but have no evidence of specific cases where reuse caused medical problems. Most writers object to reuse because the product is labeled "single use only."

Some progress is being made to resolve the overall issue of reuse. The results of an ongoing study of laboratory reuse techniques, conducted by the Association for the Advancement of Medical Instrumentation (AAMI), are expected to be released in January 1985. Personnel from the Food and Drug Administration and the Centers for Disease Control are participating with AAMI in this project.

We believe it is premature to consider any change in the regulations, as you suggest, until the results of the project are evaluated. We will keep you informed as conclusions are reached. In the meantime, we are relying on the assistance of the ESRD networks to intercede in cases of problems arising from reuse.

If you have additional questions, please contact Dr. Herbert Jacobs on extension 7-1734.

Robert A. Streimer

DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of Inspector General

AUG 1 7 1984

Mr. Robert Rosen
Chairman
Kidney Patients Association
8400 Bustleton Avenue, Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Rosen:

We have received your letter of May 31, 1984 concerning the issue of reuse of kidney dialysers by medical providers.

My office is charged with assuring the integrity of the Medicare program against possible fraud and abuse violations. However, the issue of dialyser reuse by dialysis facilities involve Medicare policy and that falls specifically within the purview of the Health Care Financing Administration (HCFA). Since HCFA has a copy of this correspondence, they will be contacting you directly.

I appreciate your reporting this matter to us and feel confident that all of your concerns will be fully addressed by HCFA.

Sincerely yours,

Donald Nicholson

Don Nicholson
Assistant Inspector General
Office of Health Financing Integrity
Office of Inspector General

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United States Senate
COMMITTEE ON LABOR AND
HUMAN RESOURCES
WASHINGTON, D.C. 20510

August 20, 1984

Mr. Perry S. Ecksel
Regional Coordinator
Kidney Patient's Association
Philadelphia, Pennsylvania 19152

Dear Mr. Ecksel:

I share your concern about the reuse of disposable mechanical devices, including kidney dialyzers and venous and arterial blood tubing sets.

I have checked with the FDA and have been told that they have received numerous letters of concern about the issue of reuse of kidney dialyzers. The policy of reuse of disposable kidney dialysis devices is not directly regulated by the FDA, although the FDA does regulate the industries involved in the production of such devices. The FDA is currently encouraging organizations such as the Association for the Advancement of Medical Instrumentation and other organizations that are included in studies of reuse of disposable items to develop national guidelines pertaining to reuse of such disposable devices. I have referred your letter to FDA for a more detailed response as to what is being done toward the development of a national policy or national guidelines.

If you are aware of specific instances of billing Medicare for new health devices when in fact re-use of disposable items has instead taken place, you should report these instances immediately to the following address:

Office of the Inspector General
Health and Human Services
Room 5250
Health and Human Services Building
330 Independence Avenue, S.W.
Washington, D.C. 20201
HOTLINE - 800-368-5779

I am sorry I don't have the staff resources to put the time into this issue that it seems to deserve. It looks like a good topic for a hearing. If things change, I'd like to look

Mr. Perry S. Ecksel
August 20, 1984
Page two

into this issue futher. Please keep in touch.

Sincerely,

Edward M. Kennedy

MINUTES

AAMI HEMODIALYZER REUSE SUBCOMMITTEE

22 August 1984
O'Hare Hilton
Chicago, Illinois

1. Opening of the meeting. The meeting was called to order at 9:00 a.m. by the cochairmen, Dr. Ronald Easterling and Dr. Albert Jarvis. Elizabeth Bridgman of AAMI staff served as recording secretary.

Committee and Subcommittee Members/Alternates Present

Lee Bland, Centers for Disease Control
Norman Deane, M.D., Renal Physicians Association
Margaret Diener, National Association of Patients on Hemodialysis and Transplantation
James Dugan, CD Medical, Inc.
Ronald E. Easterling, M.D., ASAIO
L.J. Fischbach, Renal Systems
Lois Foxen, R.N., St. Joseph's Hospital
Marilyn Case Gould, Ph.D., Associates of Cape Cod, Inc.
Albert E. Jarvis, Ph.D., CD Medical, Inc.
Stephen B. Kurtz, M.D., Mayo Clinic
Nathan W. Levin, M.D., Henry Ford Hospital
Ben Lipps, Seratronics
C.W. Miller, National Association of Nephrology Technologists
John H. Sadler, M.D., University of Maryland
James Stewardson, Cobe Laboratories
Fernando Villarroel, Ph.D., Center for Devices and Radiological Health
Elizabeth Whipple, R.N., American Nephrology Nurses Association

Guests Present

Elizabeth A. Bridgman, AAMI
Ellen Craven, CD Medical, Inc.
Paul Duke, Mesa Medical
David Kihm, Erika, Inc.
Roberta Thorpe, Erika, Inc.

2. Approval of minutes. Dr. Easterling explained that the minutes of the last meeting included comments submitted by Dr. Villarroel, which could not be discussed at that meeting due to lack of time, and should therefore be addressed at this meeting. The minutes of the 4 May 1984 meeting of the Hemodialyzer Reuse Subcommittee were unanimously approved as distributed.

3. Detailed review of draft recommended practice for reuse of hemodialyzers. The subcommittee conducted a detailed, page-by-page review of the July 1984 revision of the draft recommended practice. Comments submitted by James T. Boag (Attachment 1), Edmund G. Lowrie, M.D. (Attachment 2), A. Peter Lundin, M.D. (Attachment 3), Vincent B. Pizziconi, Ph.D. (Attachment 4) and Thomas K.

Sawyer, M.D. (Attachment 5) were distributed to those present and considered during this review. Additionally, time did not permit consideration of comments by Marie Reid. In some cases the editorial comments suggested by Ms. Reid have been incorporated into this draft. Major points of discussion and changes adopted are described below.

Foreword

The following was added to address the exclusion of blood tubing from the standard (see section 1, Scope): "The committee decided to exclude reuse of blood tubing from the recommended practice since a consensus on this issue could not be reached at this time. The committee wishes to make clear that this omission does not reflect a judgment of the merits of reusing the blood tubing."

Introduction

It was noted that both Dr. Lowrie and Dr. Villarroel had objected to negative statements regarding for-profit dialysis centers and questions raised about the motivation of physicians in the fifth paragraph of the introduction; others present at the meeting agreed that these were inappropriate for a document of this kind. It was decided to delete the third, fourth and fifth sentences of this paragraph, and to add the following sentence at the end: "This recommended practice has been written to respond to the concerns of patients, physicians and manufacturers that all reuse be conducted in a safe and effective manner." There was general agreement that the document should recognize that patients have legitimate concerns regarding reuse, and that this is a primary reason for developing guidelines.

Dr. Easterling drew attention to a number of letters from patients using reprocessed dialyzers, which had been submitted by Dr. Lundin and circulated with Ms. Bridgman's memorandum of 9 July 1984. An additional letter was handed out at the meeting (Attachment 3). Ms. Whipple stated that the letters demonstrate that allegations of improperly conducted reuse do exist. Dr. Deane observed that the most impressive letter was that which included a table correlating blood test results with the number of times a dialyzer had been used (Attachment 3). Ms. Diener noted that patients need to be aware of the AAMI guidelines, and familiar with their provisions. It was generally agreed that preparation of the guidelines was responsive to the concerns expressed by patients.

1. Scope

At the suggestion of Dr. Villarroel, the parenthetical statement in the fourth sentence of the scope will be changed to read, "(unless the manufacturer labels it for multiple use)."

Dr. Jarvis questioned the statement in 1.2 regarding the exclusion of reprocessing machines from the scope, since the machines are mentioned throughout the document. Dr. Easterling pointed out that, while reference is made to the machines, the document is not a standard for them, but a recommended practice directed to the reuse practitioner. As stated in the rationale (A1), medical device standards for reprocessing machines will be covered by a separate document.

Mr. Fischbach commented that the scope as currently worded would establish separate guidelines for blood tubing depending on whether or not the tubing was reprocessed as a unit with the dialyzer; he recommended that blood tubing be either entirely included or entirely excluded from the scope, regardless of whether it was reprocessed as a unit with the dialyzer. Some of those present felt that the current wording should be retained, with a disclaimer added to the effect that equivalent standards should be observed if tubing is reprocessed separately. Others felt it was premature to establish guidelines for reprocessing blood tubing, since the practice is not nearly as well documented as dialyzer reprocessing. The suggestion was made that the document include as much information as possible on the subject, but note that it is not comprehensive. Following this discussion, the decision was made to delete blood tubing from the scope, and explain in the rationale that the committee does not take a position for or against reprocessing tubing, but simply does not have sufficient data to include it at present. The first three sentences of A1 will be revised to read as follows: "Initially, blood tubing sets reprocessed as a unit with the hemodialyzer were included within the scope of this guideline, to accommodate reprocessing methods designed for this purpose. The committee subsequently decided to exclude blood tubing because insufficient data exists on the practice of blood tubing reuse. In making this decision, the committee did not take a position either for or against the reprocessing of tubing sets."

3. Personnel Qualifications and Training

Dr. Easterling explained that this section had been revised following the last meeting based on suggestions from NANT and subsequent comments from Michael Fisher (Attachments 2 and 3 to minutes of 4 May 1984 subcommittee meeting). Mr. Miller stated that NANT had changed its position and no longer felt that reuse technicians need be fully versed in dialysis technology.

3.2.1 Curriculum

Mr. Miller suggested a number of changes in the curriculum. After discussion, it was agreed to revise this section to read as follows:

(1) (unchanged)
(2) basic documentation requirements of the program;
(3) the operation and maintenance of the facility's specific equipment for reprocessing hemodialyzers and, if appropriate, dialysis systems and components;
(4) (unchanged)
(5) (unchanged)
(6) (unchanged)
[former item 7 deleted]
(7) risks and hazards associated with toxic substances used in reprocessing hemodialyzers, proper handling of these substances, and procedures for management of spills;
(8) (renumbered)
(9) emergency procedures as required by the facility;
(10) principles of dialysis, with emphasis on hemodialyzer characteristics.
[former item 12 deleted]

3.2.2 Levels of Training

committee also considered the question of whether there should be the right to freedom of choice not to participate in a hemodialyzer reprocessing program. Consensus could not be reached on this issue due to the conflict between individual determination and cost constraints imposed by society.) (Rettig 1983)."

5. Equipment

5.1.1 Water Systems/Disinfection

Dr. Levin pointed out that the guideline did not define "safe levels" of residual disinfectant for agents other than formaldehyde. Mr. Fischbach suggested that, given the availability of test kits for measuring disinfectant levels, the guideline could advise users to follow manufacturers' recommendations. It was recognized that there was not a consensus on what constituted a safe level of glutaraldehyde. After further inconclusive discussion, the subcommittee decided to make no change in this section, and to address safe levels of residual disinfectant in greater detail during the discussion of various disinfectants which was to take place at the AAMI conference in November.

5.2 Reprocessing Systems

The subcommittee considered Dr. Pizziconi's comment regarding microprocessor based automated systems but preferred the existing wording, and decided to make no change. The final sentence of this section was changed to make it clear that all documentation and operating procedures must be in the master record.

5.2.2 Validation Testing

Dr. Easterling observed that this section was somewhat redundant with section 9, except for pointing out the need for validation testing of both automated and manual equipment. It was agreed that the section should be retained, since it makes clear the necessity for validation testing before using the equipment on a patient. In addition, it was recognized that the word "should" in the first and last sentences should be changed to "must."

6. Physical Plant and Environmental Safety Considerations

6.1 Dressing Room Facilities

There was general agreement that this section was unnecessary, and should be deleted.

6.2 (6.1 in revised draft) Reprocessing Area

Dr. Jarvis expressed strong reservations about the adequacy of the first sentence of this section, pointing out that other reuse guidelines contain stricter requirements for the environmental safety of the reprocessing area. He recommended that the words "clean and sanitary" be used. Dr. Easterling pointed out that this is similar to the language used by the JCAH criteria. The subcommittee accepted this recommendation. The first sentence will accordingly be shortened somewhat, and the following new sentence will be added: "The area should be maintained in a clean and sanitary condition."

6.2.1 (6.1.1) Ventilation

Dr. Sawyer's proposed rewording of this section (Attachment 5) was considered, and adopted in part. It was felt that there was no need to be very specific in providing ventilation guidelines, as long as the user was referred to detailed documents available elsewhere. The final sentence of this section was accordingly replaced with the following, and the ACGIH and ASHRAE publications will be added to the list of reference documents in section 14: "Reference should be made to the Industrial Ventilation Manual of Recommended Practice compiled and approved by the American Conference of Governmental Industrial Hygienists and to ASHRAE standards in designing an adequate ventilation system." Language was also added to the rationale that conveys Dr. Sawyer's specific suggestions.

6.2.2 (6.1.2) Design Characteristics

There was general agreement that windows should not be sealed and that ceilings need not be waterproof. These requirements are for a "wet room" which is cleaned by a stream of water, a requirement that is not necessary for dialysis areas. The section will be revised to read as follows: "Windows and doors should be tight fitting. Walls and floors should be able to withstand frequent cleaning. The juncture between walls and floors should facilitate cleaning."

6.3 (6.2) Storage Area

To clarify the need for separate storage areas for different categories of dialyzers, it was agreed to modify the second sentence of this section to read as follows: "There must be separated storage areas for new dialyzers, dialyzers awaiting reprocessing and those that have been reprocessed, unless the condition of the dialyzers is clearly evident."

6.4 (6.3) Laboratory Area

With respect to the drafting note which appeared in this section, the subcommittee decided that the guideline need not address special in-house laboratory facilities.

6.5 Other Areas

This section was considered unnecessary, and the subcommittee agreed to delete it.

6.6 (6.4) Personnel Protection

Based on recommendations of Mr. Miller and others, it was agreed to revise this section to read as follows: "Durable gloves and protective clothing should be worn when handling the dialyzer during the initiation and termination of dialysis and during the reprocessing procedure. Eye protection should be worn when performing steps that may result in spills or splashes of potentially toxic materials. Impervious aprons should be worn when handling concentrated toxic substances. These agents should only be opened in areas with adequate ventilation, washing facilities, eye wash stations, appropriate respirators and spill control materials."

6.7 (6.5) Environmental Safety

At the suggestion of Mr. Bland, it was decided to make only a general reference to governmental regulations in this section, and to include specific requirements in an appendix. OSHA will be consulted to ascertain the maximum exposure levels mandated for substances other than formaldehyde. Dr. Pizziconi's proposal that all chemicals be evaluated for safe storage and handling prior to use was accepted. There was no consensus on whether monitoring of vapors should be required. It was agreed to ask appropriate speakers at the November conference to address monitoring, and for the time being to add a drafting note to the guideline indicating that additional information is being sought. Based on this discussion, section 6.7 will be revised to read as follows: "All chemicals used in reprocessing and storage should be evaluated before use for their safe storage and handling (see NIOSH/OSHA and SAX references in section 14) and there should be written procedures addressing these issues. Vapors from reprocessing materials should be maintained below potentially toxic levels. The limits set by the Occupational Safety and Health Administration (OSHA) or other regulatory agencies must be met (see Appendix F). (Drafting Note: The committee is seeking additional information before deciding whether to require monitoring of vapors, or to rely on process controls.)"

7. Reprocessing Supplies

7.1 Specifications and Testing

It was agreed that, since sampling and testing are not required for products sold specifically for use in reprocessing, the second sentence of this section should be modified to read as follows (new wording underlined): "This requirement may be determined by certification of the supplier for each shipment when the product is intended for use in reprocessing, or by relevant sampling and testing procedures, as appropriate."

7.2 Incoming Supply Control

The subcommittee accepted a proposal of Dr. Sadler that a log of substances (identified by batch) used in reprocessing a given device should be maintained. The following sentences were added at the beginning of this paragraph: "There should be a log of materials received including delivery date and lot number. When appropriate, this document should also contain the results of quality control tests."

7.3 Inventory Control

The committee accepted the suggestion of Mr. Miller that a method of documentation should be specified to aid inventory control. (Secretary's note: The suggestion of Ms. Reid has also been used to strengthen the statement). The section was rewritten as follows: "The log of materials received (see 7.2) and/or an inventory file should be used to ensure that reprocessing supplies are used on a first in, first out basis to avoid deterioration because of time in storage."

8.0 Hemodialyzer Labeling

The committee felt that the requirement for use of the reprocessed dialyzer on only one patient should be strengthened. The first sentence of the introduction was changed to "Reprocessed dialyzers must be used for the same patient."

8.3 Information Recorded

The committee felt that a record of all the uses on the label might be impractical in some cases. This first sentence was changed to "The dialyzer should be labeled with the patient's name, the number of previous uses and the date of the last reprocessing." It was also pointed out that the information suggested in this section might not fit on some dialyzers. The end of the section was changed to, "There should be a log of the results of tests, signature of the person performing various steps in the reprocessing procedure, and reference values for performance parameters. The inclusion of this information on the label may be convenient when there is sufficient room. In this case a permanent record also must be kept."

9. Reprocessing

The committee accepted a suggestion to add a sentence requiring documentation of the reprocessing procedure.

9.1 Termination of Dialysis

Dr. Easterling noted that both Dr. Pizziconi and Dr. Villarroel had submitted comments objecting to the mention of air rinsing because they feel this method is unsatisfactory. The committee disagreed, citing experience showing satisfactory results if reprocessing is begun shortly after terminating dialysis (see 9.2.1). It was decided to summarize this debate in the rationale. It was also agreed that much of section 9.1 was unnecessary, and the section was consolidated to read as follows: "At the termination of dialysis the dialysate ports should be sealed with clean caps (the blood ports should be capped with disinfected caps or the caps from the same dialyzer that have been maintained in a clean condition) and the dialyzer transported to the reprocessing area in a clean and sanitary condition."

9.2 Rinsing/Cleaning

Dr. Pizziconi's comment on 9.2.2 regarding use of an appropriate ultrafilter and his clarification of 9.2.3 were accepted.

9.3 Performance Measurements

Based on Dr. Pizziconi's suggestion, it was decided to rephrase the first sentence of this section to read as follows (new wording underlined): "Reprocessed dialyzers may show either a decrease or increase in solute and/or water transport." It was further agreed that the statements in this section more properly belong in the rationale. Regarding the remaining comments of Dr. Pizziconi on this section, it was felt that these should be considered after the November conference, when a detailed examination of quality control testing would be presented by Dr. Gotch, Dr. Pizziconi and other experts.

9.3.1 Clearance

The introductory paragraph was moved to the rationale.

9.3.1.1 Initial Validation

Ms. Foxen questioned whether it was necessary to do B-12 clearance routinely, and Dr. Easterling drew attention to Dr. Pizziconi's comments on this section. It was generally agreed that there is insufficient data at present to support Dr. Pizziconi's emphasis on large molecules. For the time being, references to B-12 will be removed from the guideline, but can be reconsidered later (e.g., after the November conference) if warranted by new data. Mr. Miller asked what constituted a "statistically significant sample" as called for in the guideline, and Dr. Easterling responded that a presentation on this issue had been planned for the November conference; it was hoped this would result in more specific recommendations for inclusion in the guideline.

9.3.1.2 Test After Each Use

Dr. Easterling expressed gratitude to Dr. Pizziconi for detailing his position on quality control testing in the comments which he had submitted (Attachment 4). Rather than discuss these comments in detail at this meeting, he suggested that it would be best to consider them following the November conference, where there will be a thorough review of these issues by Dr. Gotch and Dr. Pizziconi.

9.3.1.3 Quality Control Validation

Mr. Miller suggested that routine review of patient chemistries might reduce the frequency with which the tests specified in this section needed to be performed. Dr. Easterling observed that the requirements stated in this section do not correlate with usual practice. After discussion it was decided to modify the final sentence of this section to read as follows (new wording underlined): "If the results are consistently within the acceptable range and patient creatinine is routinely monitored, the validation may be done less frequently, such as annually. An unexplained elevation of the serum creatinine should be cause for reevaluation of the reprocessing procedure."

9.3.2 Ultrafiltration

It was again noted that Dr. Pizziconi's comments would require detailed consideration in light of the results of the November conference. Dr. Easterling pointed out that ultimately the guideline would contain an appendix giving methodologies for the various tests mentioned in the main body of the text.

9.3.3 Membrane Integrity Test

It was agreed that this test should more accurately be called "blood path integrity."

9.3.3.1 Initial Validation

Several members questioned the choice of 600 mm Hg as the air pressure at which the blood path integrity test was conducted. Mr. Lipps stated that all current hollow fiber dialyzers are rated for 500 mm Hg transmembrane pressure. It was noted that this is a design standard that might be inconsistent with advances in technology. In light of this discussion, it was decided to revise this section to read as follows: "When a new reprocessing technique is developed or a significant change is made in the dialyzer or an established technique that might affect blood path integrity, the blood compartment ideally should be subjected to an air pressure 20 percent above maximum operating pressure and the pressure decay measured. The exact pressure and pressure drop cutoff..."

9.3.3.2 Test of Each Dialyzer

Dr. Pizziconi's recommendation that each dialyzer be subjected to a mechanical integrity test after every reprocessing was not accepted. It was felt that current data did not support this approach when the leak rate of reprocessed dialyzers is equal to or less than new dialyzers.

9.4 Sterilization/Disinfection

9.4.1 Interior (Blood/Dialysate Compartment)

9.4.1.1 Germicide

Dr. Lowrie's comments (Attachment 2) regarding use of combined alcohol and formaldehyde and the effect of higher temperatures were considered. There was much discussion of establishing "4 percent formaldehyde or its equivalent" as the standard for germicide in the guideline. It was ultimately decided to revise the second and third sentences of this section to read as follows: "If formaldehyde is used as the sole disinfecting agent, a concentration of 4 percent in both the blood and dialysate compartment should be used with a minimum contact time of 24 hours at a temperature of 10-20°C (50-70°F); lower concentrations or shorter contact times may be used if adequate disinfection can be demonstrated. When other disinfectants are used, the manufacturer's instructions should be followed if the product is recommended for reprocessing, or appropriate testing done to demonstrate adequate disinfection."

9.4.1.2 Diluent

The subcommittee decided to retain the water quality requirements of this section, and to delete the drafting note identifying them as questionable.

9.4.1.3 Procedure

Dr. Villarroel had commented that the final phrase of the first sentence of this section was unclear. It was agreed to reword this sentence to read as follows: "The dialyzer should be filled with the sterilant or disinfectant solution repeatedly until the sterilant or disinfectant concentration of the effluent is within 10 percent of the original concentration." There was some feeling that 10 percent might prove to be too strict a requirement.

9.4.1.4 Monitoring

It was noted that testing each batch of disinfectant or sterilant would only be possible in manual reprocessing systems. The third sentence of this section was revised accordingly and a sentence was added which specifies the frequency of testing for the results of on-line dilution of the sterilant or disinfectant.

9.4.2 Exterior

On the recommendation of Mr. Bland the subcommittee decided to delete 2 percent glutaraldehyde as a surface disinfectant because it is too toxic to be used for this purpose.

10. Preparation for Dialysis and Testing for Potentially Toxic Residues

It was agreed that for each of the tests specified in this section, a written procedure should be available, and results should be recorded in the reprocessing record. The recommendation that there be a written record is in the introductory paragraph to this section. The recommendation that results be recorded is included in each subsection and section 10.6 of the July Revision has been deleted.

12. Quality Assurance and Quality Control

12.1 Personnel Considerations

It was agreed that, as required by JCAH, an annual rather than semiannual audit should be specified in this section.

12.2 Patient Considerations

The subcommittee felt that annual rather than quarterly audits of compliance with policy for informed consent were sufficient.

12.3 Equipment

In the second sentence from the end of this section, the subcommittee agreed to change from semiannual to annual audits of maintenance and repair policies.

13. Glossary

Dr. Easterling indicated that he would work on the additional definitions proposed by Dr. Pizziconi. At Dr. Villarroel's suggestion, the formula in the definition of "clearance, closed-loop system" was changed to read, "where b = the slope of the line generated by regression analysis of the time ..." Dr. Gould agreed to provide a definition for "endotoxin." Dr. Pizziconi's comment on the definition of "hazard" was not accepted, since it is covered in the definition of "risk." It was noted that there might be need to review the use of the terms "label" and "labeling" in the guideline, or to change the definition. Secretary's Note: "Label" has been changed to "labelling" in keeping with FDA practice. The term "label" is used in the recommended practice to designate the item carrying the labelling information.

It was felt that Dr. Pizziconi's comment on the definition of "membrane" had merit, but is addressed elsewhere in the document, e.g. in A9.3.1. Dr.

Easterling stated that he would modify the definition of the "closed loop" method for clearance in response to Dr. Pizziconi's comment about the effect of TMP on this measurement.

14. Reference Documents

It was noted that the additional reference documents offered by Dr. Pizziconi would be considered for inclusion depending on the ultimate resolution of his comments.

Rationale

It was agreed that Dr. Pizziconi's comments would be addressed following the November conference.

Other Matters

Ms. Foxen pointed out that the guideline at present does not address the question of shelf life for reprocessed dialyzers. Dr. Easterling stated that this should be discussed at the November conference in the context of comparing the various disinfecting agents.

4. Discussion of November Conference

Ms. Bridgman described plans for the AAMI conference on reuse of hemodialyzers to be held in Los Angeles on 5-6 November 1984. She noted that each of the major sessions of the conference would be followed by small workshops where detailed discussion of the provisions of the AAMI guideline could occur. (Secretary's Note: Promotional material regarding the conference has been mailed to all committee members. The latest version of the program, showing speakers either confirmed or proposed, appears as Attachment 6. It should be noted that the second day of the conference is Election Day, so those planning to attend may need to arrange for absentee ballots.)

Adjournment

The meeting adjourned at approximately 5:30 p.m.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Health Care Financing Adminis

6325 Security Boulevard
Baltimore, MD 21207

AUG 27 1984

FQA-422

Mr. Perry S. Eckeel
Kidney Patients Association
Suite 3
8400 Bustleton Avenue
Philadelphia, Pennsylvania 19152

Dear Mr. Eckeel:

Thank you for your inquiry on the reuse of hemodialyzers.

The results of a study of laboratory reuse techniques, conducted by the Association for the Advancement of Medical Instrumentation (AAMI), are expected to be released by January 1985. Personnel from the Food and Drug Administration and the Centers for Disease Control are participating in this project with AAMI.

While there have been reports of isolated problems with dialyzer reuse during the past few years, the documentation does not support a finding that reuse is detrimental to patient health and safety. In fact, there is some evidence to show that even new dialyzers may contain potentially toxic residues from the manufacturing process.

We can understand that ESRD facilities may wish to encourage the reuse of dialyzers as a cost containment measure but there is no provision in the law permitting treatment to be stopped if patients will not cooperate.

Sincerely yours,

Henry R. Desmarais, M.D.

Henry R. Desmarais, M.D.
Director
Bureau of Eligibility,
Reimbursement and Coverage

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 10 1984

The Honorable Arlen Specter
United States Senate
Washington, D.C. 20510

Dear Senator Spector:

The Congressional Liaison Office of the Department has asked us to respond to your request of July 18, 1984 on behalf of Mr. Robert Rosen, Chairman of the Kidney Patients Association of Philadelphia, Pennsylvania, regarding the reuse of kidney dialyzers.

The Food and Drug Administration's (FDA) Center for Devices and Radiological Health has been corresponding with Mr. Rosen with regard to these matters over a considerable period of time; for example, see my letter to you dated March 15, 1983 (copy enclosed). Our latest letter to him dated August 1, 1984 (enclosed) was in response to a letter which he wrote to President Reagan on May 31, 1984 (enclosed). You will note that his letter to you is an exact copy (with the exception of the last paragraph) of the letter which he sent to the President.

I believe our response to his letters fully explains FDA's position with regard to the issues he has raised in both letters.

Be assured that we will continue to provide whatever assistance we can to Mr. Rosen. However, as we have explained to him, many of his concerns are beyond the regulatory authority of FDA.

If we can be of any other assistance, please let us know.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

4 Enclosures
Submitted incoming
Cy ltr Admin/Specter - 3/15/83
Cy ltr Admin/Rosen - 8/1/84
Cy ltr Rosen/Reagan 5/31/84

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 12 1984

Mr. Robert Rosen, Chairman
Kidney Patients Association
8400 Bustleton Avenue, Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Rosen:

Thank you for your letter of August 6, 1984. Your comments will be brought to the attention of persons within the Center for Devices and Radiological Health (CDRH) who are involved in our regulatory activities associated with the reuse of hemodialyzers and other medical devices.

I understand your concerns about the reuse of hemodialyzers, but these are matters outside the jurisdiction of the FDA and must be worked out between the patient and his or her physician. As I explained in my letter to you, the FDA is doing whatever it can, within its authority, to protect the public health by developing data on the reuse of these devices and working with voluntary standards committees to develop effective protocols for proper reprocessing. We intend to continue these activities.

There is one point which needs to be clarified. You referred in your letter to our rules and regulations (which I assume to mean the Compliance Policy Guide) which you interpret to mean that a reused device is adulterated unless it is properly sterilized. The Compliance Policy Guide 7124.23 which you included in your letter to the President is dated November 11, 1977. That policy guide, however, has been superseded by Compliance Policy Guide 7124.16 dated July, 1981 (enclosed).

You will note that the new policy statement no longer refers to "adulterated devices"; rather it now states that reuse of disposable devices can affect the safety and effectiveness of devices and that information regarding such practices should be referred to the FDA. We have been operating under this Guide since its publication and our response to your letter to the President reflects that policy.

Please be assured that we remain concerned that hemodialyzers and other medical devices be used safely and effectively. We are working, within our authority, to insure that the public health is not compromised by improper use or reuse of these devices.

If we can be of any further assistance, do not hesitate to contact us. However, to facilitate future correspondence, I suggest you direct your inquiries to Mr. Lawrence Kobren, CDRH, HFZ-240, 5600 Fishers Lane, Rockville, Maryland 20857, who chairs a committee which advises me about the reuse of medical devices.

Sincerely yours,

John C. Villforth
Director
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

September 17, 1984

Mr. Robert Rosen
6332 Powder Horn Court
Bensalem, Pennsylvania 19020

Dear Mr. Rosen:

I have been asked to reply to your letter of July 25, 1984 to the Department of Health and Human Services, in which you asked for clarification of the Food and Drug Administration's Compliance Policy Guide 7124.23 dated November 11, 1977.

That guide has been superceded by Compliance Policy Guide 7124.16 dated July 1, 1981. I have enclosed a copy of that guide for your examination.

Both guides place the responsibility for reuse on the institution or practitioner and both indicate that they should be able to demonstrate: (1) that the devices can be adequately cleaned and sterilized, (2) that the physical characteristics or quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use. The major difference between the two is in the policy statement. The current version's only requirement is that information developed regarding reuse be brought to the attention of the Center for Devices and Radiological Health (formerly the Bureau of Medical Devices) for evaluation. There is no reference in the current policy to adulterated devices.

I hope this clarifies for you the FDA's position with respect to our compliance policy with regard to reuse. The FDA takes no position with respect to the decision to reuse a medical device. That decision is between a physician and the patient, and the FDA will not interfere with that process.

With respect to your final point, the FDA does not require that the manufacturer label his sterile disposable device "for one time use only." Manufacturers who label their device with this or similar statements do so on their own volition because they believe that they cannot guarantee that a reprocessor would follow their instructions. This presumed liability forces the manufacturer to put "for one time use only" or equivalent on their labeling.

If I can be of any further assistance, please contact me.

Sincerely yours,

Lawrence Kobren
Chairman Reuse Committee
Center for Devices and
Radiological Health

Enclosure

Kerry [illegible]
HFZ-240

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the General Counsel
Food and Drug Division

Memorandum

Date September 25, 1984

From Ann M. Witt AW
Through: Thomas Scarlett Tom Scarlett

Subject Reuse of Medical Devices; Adequate Directions for Use

To John Villforth
Director, Center for Devices and Radiological Health

This memorandum responds to your request of July 3, 1984, for a legal opinion as to whether FDA can require manufacturers of medical devices currently labeled "for single use only" to provide adequate directions for reuse. For most devices, it is unlikely that FDA could sustain such a requirement, if imposed under a theory based on 21 CFR 801.4 that wide reuse of a disposable device by consumers constitutes a new "intended use" of the device for which adequate directions are required. The courts have held that an "intended use" could be established through consumer use only if consumers used the device for the use in question "nearly exclusively"; moreover, certain factors suggest that the agency might not prevail in requiring directions for reuse even with a product as frequently reused as hollow fiber dialyzers.

Even if the agency could establish a new intended use on the basis of consumer reuse, such a showing would necessarily also establish that the device, when labeled for reuse, was a new device requiring the submission of a PMA. Where a product is so frequently reused that there exists the possibility of bringing a legal action to establish a new intended use, FDA may, under certain circumstances, be able to "encourage" manufacturers to voluntarily provide instructions for reuse in return for not requiring the submission of a PMA. The Health Care Financing Administration might also, through Medicare reimbursement restrictions, provide an avenue for encouraging manufacturers to provide adequate directions for reuse.

A. Reuse As A "New Use" Of A Device

Section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) provides that a device is deemed to

84-10-085

be misbranded unless its labeling provides "adequate directions for use." It is well established that a vendor (e.g., a manufacturer or distributor) of a device must provide adequate directions for all uses intended by the vendor. Evidence of the vendor's intent is not limited to its subjective claims; that intent may also be established by objective evidence such as labeling, promotional claims, advertising, "and any other relevant source." See, e.g., Hanson v. United States, 417 F.Supp. 30, 35 (D. Minn.), aff'd, 540 F.2d 947 (8th Cir. 1976).

1. Establishing "Intended Use" Through Consumer Use.

a. Section 801.4

It has been suggested that manufacturers of "disposable" devices that are being widely reused by consumers should be held responsible for providing adequate directions for reuse, on the ground that a manufacturer intends not only the uses for which a product is labeled or promoted, but also those for which it knows the product is actually being used. Section 801.4 of FDA's device labeling regulations appears to lend support to this argument. The regulation, which defines "intended uses" for certain purposes, states, in part:

> The words "intended uses" or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally reponsible for the labeling of devices.
>
> .... The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he

> to required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.

Despite the apparent applicability of § 801.4 to consumer reuse of devices, there are significant limitations on the extent to which FDA can rely on the regulation to require manufacturers to provide adequate directions for reuse.1/

It is unlikely that a court would interpret § 801.4 to impute intent in most instances in which a manufacturer learns of an unpromoted consumer use of its device. The validity of such an interpretation would be judged against 1) the original intent of the regulation, 2) the case law interpreting "intended use" in related contexts, and 3) the consistency of the agency's interpretation of its authority in this area.

The background documents underlying the original regulation from which § 801.4 is adapted state that the regulation was intended to cover situtations "in which an article is properly labeled by its manufacturer with the uses he intends but which is later offered for different uses by distributors or sellers." (Copy attached.) Thus, the background of § 801.4 does not provide much support for requiring adequate directions for use based solely on consumer use. Instead, the background documents suggest that the definition was

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1/ § 801.4 does not apply, by its own terms, to adequate directions for use of prescription devices. The regulation expressly applies to §§ 801.5 (adequate directions for lay for lay use), 801.119 (exemption from 520(f)(1) for certain in vitro diagnostics), and 801.122 (exemption for devices intended for use in manufacturing other devices). However, although § 801.4 is not expressly applicable to § 801.109, the regulation exempting prescription devices from section 502(f)(1) of the Act (but requiring instructions for professional use), it may be reasonably argued that the enumerated sections in § 801.4 are not exclusive and that the definition of "intended use" should apply at least in any context involving "adequate directions for use."

intended to cover uses that are promoted at some point in the chain of distribution.

In addition, the agency has not established a consistent interpretation of its authority to regulate consumer uses of regulated products, nor does the case law defining the evidence necessary to establish "intended use" support a broad interpretation of § 801.4. These two subjects are discussed in the next section.

b. FDA's Historical Interpretation Of Its Authority and the Case Law.

The agency has occasionally suggested that it has authority under the Act to require that manufacturers provide adequate directions for an unlabeled consumer use of a regulated product. However, there is only limited support for this position in the case law.2/

A 1972 notice of proposed rulemaking concerning prescription drugs prescribed for unapproved uses suggested that FDA can require a manufacturer to provide adequate directions for an unapproved use if it becomes widespread:

> *Where the unapproved use of an approved new drug becomes widespread* or endangers the public health, the Food and Drug Administration is obligated to investigate it thoroughly and to take whatever action is warranted to protect the public. *Several alternative courses of action are available to the Food and Drug Administration* under these circumstances, depending upon the specific facts of each case. *These actions include: Requiring a change in the labeling to warn against or to approve the unapproved use, seeking substantial evidence to substantiate the use*, restricting the channel of distribution, and even withdrawing approval of the drug and removing it from the market in extreme cases. [Emphasis added.]

2/ The agency does have authority to require warnings *against* unapproved consumer uses. Section 201(n) of the Act; *see*, *e.g.*, 21 CFR §§ 201.57(c)(3)(iv) and (e).

37 Fed. Reg. 16053, 16054 (August 15, 1972). The position stated in the proposal was controversial, however, and the proposed rule was never adopted.

I am aware of only three instances in which FDA has "invited" a drug manufacturer to provide adequate directions for a second use of an approved drug, based on widespread consumer use.[3] However, two manufacturers did so voluntarily; a third was allowed to add a warning against the use. Thus, FDA's authority to require such action has never been tested. Moreover, it is unclear, even in these cases, whether FDA believed it had authority to compel the requested actions from manufacturers. It appears that the agency believed that the manufacturer was free to choose between providing adequate directions for the new use and adding a warning against the use. See *New Drugs Used for Nonapproved Purposes Methotrexate for Psoriasis: Hearings Before a Subcomm. of the Comm. on Government Operations*, 92d Cong., 1st Sess. 27 (1971) (testimony of FDA Chief Counsel William Goodrich). Thus, FDA has not established a consistent interpretation of its authority to regulate unapproved consumer uses that would support a broad interpretation of 21 CFR 801.4.

Moreover, the case law defining "intended use" does not support as broad an interpretation of FDA's authority to require a manufacturer to substantiate and provide adequate directions for a consumer use as the statement in the 1972 notice. (It is worth noting that FDA's attempt to enforce another of the remedies proposed in the 1972 notice, limiting the channels of distribution, was struck down in *American Pharmaceutical Manufacturers Ass'n* v. *Weinberger*, 377 F.Supp. 824 (D.D.C. 1974), *aff'd sub nom. American Pharmaceutical Manfuacturers Ass'n* v. *Mathews*, 530 F.2d 1054 (D.C. Cir. 1976).)

The few courts that have addressed the issue of whether an "intended use" can be established through evidence of consumer use (in the context of whether a product was intended as a "drug" or "device") have not ruled out the possibility of reliance on consumer use. *See Action on Smoking and Health* v. *Harris*, 655 F.2d 236 (D.C. Cir. 1980); *National Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d 325 (2d

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[3] The drugs in question were tolmetin, methotrexate, and xylocaine.

Cir. 1977); *Millet, Pit & Seed Co., Inc.* v. *United States*, 436 F.Supp. 84 (E.D. Tenn. 1977), *vacated on other grounds*, 627 F.2d 1093 (6th Cir. 1980). However, these courts have imposed an extremely rigorous test: where there is no evidence that a vendor has promoted a product for a specific use, evidence of consumer use can establish the requisite intent only if consumers use the product "nearly exclusively" for the use in question. *Action on Smoking and Health*, 655 F.2d at 240; *National Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d at 334.[4]

In order to establish that devices are "intended" for reuse under the narrow reading of FDA's authority adopted by the courts, FDA would have to be able to prove that the the devices are almost exclusively reused by consumers. This test might be met in a case like that of hollow fiber dialyzers, where over 90% of the devices are being reused, if there were objective evidence (e.g., a valid consumer survey) substantiating that usage. Reuse by a smaller percentage of consumers would, however, probably fail to establish the requisite "intended use."

However, it must be emphasized that even for a device as widely reused as hollow fiber dialyzers, it is not at all clear that FDA would prevail in an enforcement action to require adequate directions for use. In none of the cases suggesting that an "intended use" could be established through consumer use has a court found that the test was met. Under these circumstances, it is impossible to predict what evidence would be sufficient to satisfy a court that the test had been met.

A second factor casting doubt on the likelihood of success in an enforcement action is that in all previous "intended use" cases there has been a strong suggestion, express or implied, that the manufacturer was knowingly profiting from the unapproved consumer use, without assuming legal responsibility for the use. In this case, for the first time, there could be little suggestion that manufacturers were profiting from reuse. On the contrary, reuse of their products is to their economic disadvantage. Thus, forcing these manufacturers to assume responsibility for the risks of reuse is far less compelling from an equitable perspective than it has been in previous cases.

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[4] The court in *National Nutritional Foods* also required that FDA establish a lack of other recognized uses, in that case non-drug uses, for the product. It is unclear how, or if, such a requirement would apply in the context of reuse, because a product must necessarily be used once, i.e., as labeled, before it can be "reused."

c. New Use Requires a PMA

Even if the strict standard set by the courts for establishing a new intended use can be met for certain devices, there is an additional problem with this approach. If FDA is successful in establishing that a manufacturer intends his device for a new use, namely reuse, the agency will thereby also have established that the manufacturer is marketing a "new" device. Unless there is a preamendments device to which the new device is substantially equivalent and that was marketed for reuse, the new device will be automatically classified in class III under section 513(f)(1) of the Act, and the manufacturer will be required to obtain premarket approval for, or reclassification of, the new use.

Thus, except in extremely rare cases, an FDA decision to require a manufacturer to provide adequate directions for a new use will necessarily entail the submission of a PMA establishing the safety and effectiveness of reuse. (This would be a particularly burdensome requirement for class II or preamendments class III devices, because there would be no existing PMA's to supplement.)

Furthermore, once a requirement of premarket approval for reuse has been established, the manufacturer could resist the entire process. Although FDA can require the submission of a PMA, it cannot require the manufacturer to provide sufficient information or conduct adequate studies on which to base approval. Where, as in this case, it is in the manufacturer's interest not to provide adequate directions for reuse, the manufacturer may very well submit a PMA so poor that FDA will be forced to disapprove it. If the PMA for the new use were disapproved, labeling that included directions for reuse would render the product misbranded.

In summary, FDA's authority to require adequate directions for reuse, if based on a theory that consumer reuse establishes a new intended use of the device, is probably limited to cases in which FDA can show that consumers reuse the device in question "nearly exclusively." Such a showing, however, would be tantamount to a determination that the device, when intended for reuse, was a new device requiring premarket approval. If a manufacturer then submitted a PMA that could not be approved because it did not show that reuse was safe and effective, FDA would be unable to achieve its original purpose of requiring the manufacturer to provide adequate directions for reuse.

B. Alternatives to Establishing A New Intended Use.

I have considered the possibility of regarding reuse for the labeled indication not as a "new use" but simply as a method of administration of, or manner of preparation for, the existing intended use. Methods of administration, and preparation, like dosages, are among the types of instructions that fall within the regulatory definition of "adequate directions for use." 21 CFR 801.5 and 801.109.

If viewed this way, FDA would not have to establish a new intended use on the part of the manufacturer in order to require that the labeling bear adequate directions for reuse. Instead, FDA would simply have to establish, through notice and comment rulemaking,[5] that directions for reuse are among the categories of information about an existing use of a device that constitute "adequate directions" for that use.

However, this approach to the problem has a fatal defect: a regulation requiring adequate directions for reuse would not provide FDA with any authority to require that manufacturers submit sufficient data to establish that reuse, as directed, was safe and effective. Without such authority,

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5/ The categories of information that make up "adequate directions" are established by regulation. The device labeling regulations currently define adequate directions for lay use to *include* (the regulation does not purport to contain an exclusive description): quantity of usual dose, frequency and duration of administration, time of administration, route or method of administration, and preparation for use. 21 CFR 801.5. Prescription devices must contain information including indications, effects, routes, and any relevant hazards, contraindications, side effects, and precautions. 21 CFR 801.109.

the agency would be unable to justify the requirement itself.[6]

3. Another Alternative

Because FDA's authority to require adequate directions for reuse is limited, the Center may wish to consider requesting the Health Care Financing Administration (HCFA) to provide assistance in changing manufacturers' minds about the benefits of providing directions for reuse. HCFA, as part of it its administration of the Medicare program, regularly places restrictions on the medical services and products for which it will provide reimbursement. These restrictions are generally intended to reduce medical costs. Reuse of devices is a cost saving technique. HCFA might therefore be willing to consider providing an incentive for reuse by limiting reimbursement for potentially reuseable devices to those devices for which manufacturers provide adequate directions for reuse.

If a reimbursement restriction were imposed, FDA's only obligation would be to assure that there were adequate data to establish the safety and effectiveness of the directions for reuse through review of 510(k)'s and PMA's where necessary, and, if desired, to provide guidance to manufacturers on preparing those submissions. Please note, however, that the possibility of reimbursement restrictions has not been raised with HCFA; it is merely a theoretical possibility. If you wish to pursue this option, please let this office know and we will explore it further with the Department before you approach HCFA.

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[6] Nevertheless, this conceptual approach suggests a possible position for negotiation with the manufacturers of hollow fiber dialyzers (and any other manufacturers of devices being reused in the same proportion). If the agency were prepared to bring an enforcement action against these manufacturers to establish that the devices were "intended for" reuse, it could offer the manufacturers an opportunity to "voluntarily" relabel the products for reuse and submit supporting data, with the understanding that if they did so, the agency would not view reuse as a new use and thus would not require the submission of a PMA. This could be done, however, only if the agency could conclude that the device when labeled for reuse was substantially equivalent to a preamendments device.

If you would like to discuss any of these ideas further, please call me at 443-4390.

cc: Linda Horton
Mike Landa
Kathy Schroeher
Don Segal
Mark Heller

DEPARTMENT OF HEALTH AND HUMAN SERVICES
HEALTH CARE FINANCING ADMINISTRATION

6325 Security Boulevard
Baltimore, MD 21207

FQA-422

SEP 28 1984

Mr. Perry S. Eckael
Kidney Patients Association
8400 Bustleton Avenue
Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Eckael:

This is in further response to your letters inquiring about regulatory standards for renal mechanical devices. You asked whether products originally labeled for single use constitute illegal experimentation when used more than once. You also expressed concern about reprocessing devices using various cleaning agents.

When we received your letter, we immediately got in touch with the Food and Drug Administration (FDA) about the issues you raised. They advise us that a request for similar information was made by Mr. Robert Rosen, Chairman of your organization, in a letter addressed to President Reagan. The director of the Center for Devices and Radiological Health, responded to Mr. Rosen on August 1, 1984.

Under the law, the Health Care Financing Administration is not authorized to recommend or prevent reuse of renal devices. Guidelines established by the FDA and the Association for the Advancement of Medical Instrumentation (AAMI) will be released and available after January 1985 and will address all of your concerns. We are sorry that we do not have any new information to report at this time.

Sincerely yours,

Henry R. Desmarais, M.D.

Henry R. Desmarais, M.D.
Director
Bureau of Eligibility,
Reimbursement and Coverage

MINUTES
AAMI HEMODIALYZER REUSE SUBCOMMITTEE

7 December 1984
Sheraton Washington Hotel
Washington, DC

1. Opening of the meeting. The meeting was called to order at 10:10 a.m. by the cochairmen, Ronald E. Easterling, M.D., and Albert E. Jarvis, Ph.D. Elizabeth Bridgman of AAMI staff served as recording secretary. Those present introduced themselves.

Committee and Subcommittee Members/Alternates Present

Vera Buffaloe, Cobe Laboratories
Ronald Easterling, M.D., ASAIO
L.J. Fischbach, Renal Systems
Jerry Fisher, Travenol Laboratories
Lois Foxen, R.N., St. Joseph Hospital
Frank Gotch, M.D., R.K. Davies Medical Center
Albert Jarvis, Ph.D., CD Medical
Stuart Kaufer, NAPHT
Lawrence Kobren, FDA/CDRH
Ben Lipps, Seratronics
Martin Roberts, Organon Teknika
John Sadler, M.D., University of Maryland
Tom Sawyer, M.D., Northwest Kidney Center
Luke Schmieder, Mesa Medical
David Wagner, Computer Dialysis Systems

Guests Present

Rose Annis, Alcide Corporation
Elizabeth Bridgman, AAMI
Roberta Thorpe, Erika

2. Review of draft recommended practice for reuse of hemodialyzers. The subcommittee conducted a detailed page-by-page review of the September 1984 revision of the draft recommended practice. Comments previously circulated from David A. Berkowitz (ECRI), Martin Favero, Ph.D. (Centers for Disease Control), Marilyn Gould, Ph.D. (Associates of Cape Cod), and Harry Kaufman (Alcide Corporation) were considered in the course of this review, as were comments from Frank Gotch, M.D. which were distributed at the meeting (see Attachment 1).

Dr. Easterling pointed out that issues raised during the November 1984 AAMI conference on reuse of hemodialyzers, such as processing performed outside the dialysis facility and QC and QA aspects of reuse in home dialysis, should also be addressed during the course of this review. Also, regarding Mr. Kaufman's comment on use of the terms "sterilant" and "disinfectant," Dr. Easterling suggested that the term "germicide" be adopted throughout the document; there was general agreement with this proposal, and the draft has been amended accordingly.

2. Records. Regarding Mr. Kaufman's comment on the need for trend data on complaints, it was agreed to add a statement to 2.4 recommending that the complaint file be reviewed periodically for trends. In response to the comments by Mr. Berkowitz a new section was added concerning personnel health records.

2.1 Master Record. It was pointed out that the master record is the one place where all records should appear. Dr. Easterling indicated that he would prepare revised wording for this section that would address multiple records.

2.3 Equipment Maintenance and Material Quality Record. In response to Mr. Berkowitz's comment on this section, it was agreed that Dr. Easterling would expand this section to include environmental control equipment.

4.1.2 Contraindications. At Dr. Sawyer's suggestion, it was decided to modify item (2) of this section to mention abnormal liver function tests "indicative of" (rather than "consistent with") viral hepatitis.

4.2 Informed Consent. Mr. Kobren raised a question concerning who obtains informed consent, and noted that informed consent has a regulatory connotation. Dr. Easterling replied that informed consent is a common part of medical practice and therefore an appropriate subject to be addressed by this document.

5.1 Water Systems. Mr. Kaufer recommended that this section include a statement about the need for water for reprocessing to be separate from water used for dialysis in the case of a central delivery system. He noted that in a recent incident in Atlanta patients had received formaldehyde due to this problem. Dr. Easterling asked Mr. Kaufer to provide the committee with any written reports on the Atlanta incident, for referencing in the rationale. It was agreed to add the following sentence at the beginning of 5.1: "The design of the system must prevent cross-contamination between water used for reprocessing and water used for dialysis."

5.1.1 Disinfection. Pursuant to the concerns raised about section 5.1, the subcommittee decided to add a requirement for testing for residual germicide by adding the following words at the end of this sentence: "... as demonstrated by an appropriate test."

5.1.2 Testing Water Quality. Reference to pyrogen contamination was deleted from this section pursuant to the changes in sections 9.2.2 and 9.4.1.2.

5.3 Environmental Control Equipment. In light of Mr. Berkowitz's comment on this section, there was some discussion of the frequency of inspection of environmental control equipment. It was agreed that Dr. Easterling provide wording to address the issue, and the recommended practice has been amended in accordance with his proposal.

6.1 Reprocessing Area. It was pointed out that the reference in the final sentence of this section should be changed to "See 6.5".

6.1.1 Ventilation. With respect to the comment of Mr. Berkowitz on this section, Dr. Sawyer said that the ASHRAE terminology is "cubic feet per minute" and that neither term is accurate. He felt that it would be preferable to state that the room not be pressurized with respect to surrounding areas. Mr. Fischbach observed that meeting the performance standard is the most important factor. Dr. Sawyer agreed to attempt to redraft the section after referring to the Department of Health and Human Services document referenced by Mr. Berkowitz. Ms. Bridgman stated that she would obtain a copy of the HHS document for reference. (Secretary's Note: The document has been ordered, but is currently out of stock; it will be made available to Dr. Sawyer as soon as it is received.)

6.2 Storage Area. In response to the comment of Mr. Berkowitz, it was agreed to add a reference to NFPA 30 or other appropriate regulations.

6.4 Personnel Protection. The subcommittee agreed to modify the final sentence of this section as proposed by Mr. Berkowitz. Mr. Berkowitz's comment regarding signs was not accepted because it was the sense of the subcommitee that there are already a great many signs within a dialysis unit and in any case in an emergency situation there would be no time to make reference to signs. It was, however, agreed to add to section 3.2.1 on the training curriculum mention of the use and location of safety equipment.

6.5 Environmental Safety. There was some discussion of the comment from Mr. Berkowitz regarding environmental monitoring and employee medical surveillance, and Dr. Easterling suggested that perhaps a frequency of testing should be mentioned in section 6.5, which could then be referenced in section 5.3. It was decided to delete the drafting note in section 6.5 because the recommendation to follow appropriate standards covers this issue. Ms. Bridgman was asked to obtain the OSHA regulation mentioned by Mr. Berkowitz so that it could be appropriately referenced. Regarding Mr. Berkowitz's recommendation on preplacement medical examinations, there was general agreement that this document was not intended to deal with this type of issue, and that it should not be addressed here, except to reference relevant OSHA regulations.

7.1 Specifications and Testing. Dr. Easterling reported that at the AAMI conference in November the suggestion had been made that this section require that any testing be performed by a skilled and knowledgeable individual. It was felt that this issue was adequately addressed by the reference to "relevant sampling and testing procedures", but that the phrase "by trained personnel" would be added to this sentence for clarification. Further it was agreed that formaldehyde should be of USP quality or better to avoid contaminants that may occur in industrial grades.

7.2 Incoming Supply Control. It was agreed to modify the final sentence of this section to state that reprocessing materials should be received and inspected as well as released for use only by authorized personnel.

8.2 Label Composition. In response to Mr. Berkowitz's comment, it was agreed to modify the first sentence of this section to read as follows: "Markings should be resistant to normal reprocessing and dialysis procedures."

8.3 Information Recorded. It was felt that the concerns expressed by Mr. Berkowitz were already addressed by the rationale for this section.

9.1 Termination of Dialysis. Dr. Easterling reported that it had been recommended at the November conference that the material about caps should be moved to section 9.4.1.3 and that this section should be modified by the addition of the words "if appropriate", as follows: "If appropriate the dialyzer should be transported to the reprocessing area in a clean and sanitary manner." In explanation of this change it would be noted in the rationale that there are situations where reprocessing is integral to the dialysate supply system.

9.2 Rinsing/Cleaning.

9.2.1 Dr. Sawyer questioned the rationale for the 10-minute and 6-hour limitations in this section, pointing out that the first is too short and the second too long considering the 20-30 minute bacteria generation periods. It was agreed to modify this section to be more general, as follows: "Reprocessing of the dialyzer should begin within a time capable of producing a reprocessed device which meets the requirements of section 9.3." It was also agreed that the discussion deleted from 9.2.1 should be placed in the rationale.

9.2.2 Dr. Easterling recalled that the general feeling at the November conference was that rinsing/cleaning should be done with RO quality water. The subcommittee discussed this recommendation, but decided not to limit the procedure to RO quality water. There was considerable discussion of the use of the LAL test, with several members questioning its value. Dr. Easterling pointed out that the use of this test was based on the Favero and Peterson reference in section 14. Dr. Sawyer suggested that if this test were to be referenced, then the document should specify that the CDC procedure be followed. Dr. Jarvis stated that he would accept the removal of this test only if the CDC were agreeable. Dr. Easterling suggested that in the absence of a consensus the document could state that if testing is done it should be done in this manner. He recommended that the question be referred to both Dr. Favero and Dr. Gould for response. (Secretary's Note: The draft has been revised to indicate the CDC recommendation without further elaboration.)

Dr. Gotch pointed out that for years most practitioners of reuse have not conducted LAL testing and that as presently worded the AAMI recommended practice would add a new test to common reuse procedure. In the course of further discussion, it was pointed out that experts differ on the question of whether the LAL test is reproducible. Dr. Easterling noted that the FDA has approved the LAL test as a suitable replacement for the rabbit test, and that the National Kidney Foundation recommendations now include the LAL test. Ms. Buffaloe pointed out that the FDA has a guideline on the LAL test, and Mr. Kobren stated he would obtain this guideline for reference by the subcommittee. No final conclusion on use of the LAL test was reached, pending additional discussion at future subcommittee meetings based on additional expert opinion. (Secretary's Note: The draft has been changed to indicate the CDC's recommendation without further elaboration.)

9.3.1 Clearance. Dr. Gotch drew attention to his written comments (Attachment 1), pointing out that they were a restatement of the presentation he had made at the November conference stressing reliance on cell volume rather than ultrafiltration rate as the key parameter to be tested. Dr. Sawyer commented that fiber bundle volume is the simplest test to perform, but noted that it is a "secondary" measurement. The committee agreed that the UF rate test proposed by Dr. Pizziconi can be used but that there is greater variability than with the FBV test. It was decided not to include reference to the UF rate test in the recommended practice and to revise the rationale to reflect the concerns of Dr. Pizziconi. Dr. Easterling pointed out that there is a general statement concerning clearance in section 9.3.1, and that the plan was to include a recommended methodology for the test in an appendix. (Secretary's Note: The appendix has been deleted since this material is more properly the subject of a technical information report.)

9.3.1.3 Quality Control Validation. Dr. Gotch stated that the most important factor is that FBV be done reproducibly. He said that replicate FBV measurements on the same device should not vary by more than ± 2 ml, replicate clearance measurements should be within 5 percent, and the technique of measuring cell volume should be verified at least every month (in manual reprocessing, this is a function of personnel). A question was raised as to whether accuracy or precision was being addressed here, and Mr. Roberts stated that it was precision since it deals with repeated measurements. In conclusion, it was agreed that section 9.3.1.3 would require a major revision in the light of this discussion.

9.3.2 Ultrafiltration Rate. The point was made that UF rate is very difficult to measure and that a methodology is needed for inclusion in the appendix. Some members questioned whether this parameter can be measured in a clinical setting with precision. It was decided to change this section to warn against using in vitro ultrafiltration rate as a guide to in vivo ultrafiltration rate.

9.3.2.2 (now combined with 9.3.2) Quality Control Validation. Dr. Gotch stated that most dialysis units do not have ultrafiltration rate data on the first use of dialyzers and would have difficulty developing it. After some discussion, it was agreed to change this section to address process control when expected clinical results are not achieved.

9.3.2.3 (now 9.3.2.1) In Vitro Test for Each Dialyzer. A question was raised as to why in vitro ultrafiltration should be performed. Mr. Lipps explained that this test would enable the user to know whether major shifts are occuring in membrane properties which would not be picked up in the volume test. Some people use this as the primary reject criterion, while others use it as a secondary criterion. Dr. Easterling stated that the rationale would be modified to explain why the limits in this section are so great. It was also agreed to delete the last paragraph of the rationale, A9.3.2.

9.3.3 Blood Path Integrity Test. The subcommittee considered a clarification of this section which had been proposed at the November conference, but concluded that it offered no improvement over the current wording. (Secretary's Note: On rereading, the chair took the liberty of making minor changes to clarify this section.)

9.4 Sterilization/Disinfection. The subcommittee felt that Mr. Berkowitz's comment regarding ethylene oxide sterilization was not relevant because the recommended practice does not address blood tubing. It was also pointed out that the document does include general environmental controls.

9.4.1.1 Germicide. With reference to Mr. Kaufman's comments, Ms. Buffaloe pointed out that their intent was to make the recommended practice consistent with regulations. After some discussion, it was decided to adopt Mr. Kaufman's proposals with some modifications, so that this section would be reworded to read as follows:

> "Chemical germicides used for disinfection of hemodialyzers must have been shown to be effective when tested in a variety of dialyzers artificially contaminated with appropriate microorganisms, including the highly resistant water adapted forms, at the concentration, temperature, and contact times recommended by the manufacturer for dialyzer processsing. If formaldehyde is used as the sole disinfecting agent, the Centers for Disease Control recommends a concentration of 4 percent in both the blood and dialysate compartment should be used with a minimum contact time of 24 hours at a temperature of 10-20 °C (50-70 °F); lower concentrations or shorter contact times are appropriate if adequate disinfection can be demonstrated. When other disinfectants are used the manufacturer's instructions should be followed if the product is recommended for reprocessing, or appropriate testing done to demonstrate adequste disinfection. The chemical germicide must not damage the integrity of the dialzyer and must rinse out of the dialyzer to below known toxic levels within a rinse out period established for the specific germicide (See 10.4)."

Regarding the 4 percent formaldehyde concentration, it was recalled that Dr. Favero had stated at the close of the Los Angeles conference that he believed mycobacteria could be a problem even if the AAMI water requirements are met, and that based on his survey of dialysis centers many do have this bacteria in their water. The above revision of section 9.4.1.1 incorporates a reference to the CDC in order to identify the origin of the recommendation on formaldehyde concentration. It was agreed that an inquiry be directed to Dr. Favero to determine whether the CDC has any data or evidence of clinically significant mycobacterial infection other than the Baton Rouge incident.

(Secretary's Note: Subsequent to the committee meeting, Dr. Lowrie's comments regarding evaluating toxicity of germicides other than formaldehyde (Attachment 3) were received. It was concluded that there was insufficient data available to the committee to be specific and the newer germicides must be reviewed by the FDA. It was felt that the last sentence of this section adequately addresses this issue.)

9.4.1.2 Diluent. It was noted that this section again raises the question of pyrogenicity (see 9.2.2). (Secretary's Note: The draft has been revised to indicate the CDC recommendation without further elaboration.)

9.4.1.3 Procedure. It was agreed to modify the second sentence of this section to read as follows: "The ports of the dialyzer should be disinfected after filling with sterilant or disinfectant and then capped with new or disinfected caps."

9.4.1.4 Monitoring. Dr. Gotch rasied a question regarding the frequency of testing for the presence of disinfectant as specified in the final sentence of this section. It was agreed to modify this to specify testing a random sample rather than testing each dialyzer. Dr. Easterling pointed out that the use of dye is not at present mentioned at all in the document; he stated that he would mention in the rationale that dye is used, but that no consensus currently exists regarding its possible effect. (Secretary's Note: Following the meeting, Dr. Lowrie offered the commentary which appears as Attachment 2.) Dr. Gotch expressed concern as to whether monthly testing for bacteriological contamination as specified in 5.1.2 was sufficient. He pointed out that automatic devices can give a false sense of security.

10. Preparation for Dialysis and Testing for Potentially Toxic Residues. With respect to Mr. Berkowitz's comment recommending the use of a "pre-use checklist", the committee decided that this is one way to achieve the desired result, but that it should not be a recommendation in the recommended practice.

10.2 Verification of Patient Identification. Regarding Mr. Berkowitz's comment, it was pointed out that the question about informed consent is not whether or not to have informed consent but whether it is appropriate to single out reuse of the dialyzer from the rest of the dialysis procedure for specific informed consent. It was felt that this issue is irrelevant in regards to having the patient identify his or her name on the dialyzer.

10.4.1 Testing for Residual Sterilant or Disinfectant. Mr. Berkowitz's comment on this section had been referred to Dr. Gotch, who reviewed the Lewis, Ward, and Kerr study, noting that the principal issue is the level of anti-N-like antibodies. Dr. Gotch made reference to a study published in the ASAIO Transactions six years earlier by Koch et al which showed that a residual formaldehyde level of less than 10 ppm does not induce anti-N-like antibodies. He noted also that the study upon which the recommendation cited by Mr. Berkowitz is based only dealt with levels of 1 ppm or less compared with a mean of 8 ppm (2-13 ppm). It was agreed to leave section 10.4.1 unchanged, but to expand the rationale to respond to the comment of Mr. Berkowitz.

10.4.3 Validation of Elution and Priming Procedure. It was agreed to modify the first sentence of this section to read as follows: "...the maximum level of germicide is achieved at least at the 95 percent confidence level."

11.1.1 Fever and Chills. Dr. Sawyer observed that temperature should be recorded for patients who are not reusing dialyzers as well as those who reuse. It was decided to add the following to the end of the first sentence of this section: "for new and reused dialyzers."

12. Quality Assurance (QA) and Quality Control (QC). In response to Mr. Kaufman's comment, it was agreed to change the definition of QC in the second sentence of this section by replacing the word "verification" with the word "determination." Regarding Mr. Kaufman's recommendaton for review of trend data relating to complaints, Dr. Easterling stated that he would add a paragraph and other revisions addressing this issue to section 12.

13. Glossary

Closed Loop System. It was noted that brackets needed to be added to the equation in this definition.

With respect to Mr. Kaufman's comment on the EPA definition of a sterilant, it was generally agreed that this definition was not relevant in the context of the recommended practice.

Dr. Gould's proposed definitions of the terms lipopolysaccharide, endotoxin, and pyrogen were adopted with slight modifications, as presented below, and with the recognition that the relevance of these terms to the document was still subject to further consideration in light of the final decision yet to be reached on the LAL test.

Lipopolysaccharide (LPS): Group of structural molecules unique to the outer membrane of gram-negative bacteria. Purified LPS is O-antigen and bacterial endotoxin.

Endotoxin: Toxic substance (lipopolysaccharide) from gram-negative bacteria that has a broad spectrum of biological activities, including pyrogenicity.

Pyrogen: A fever causing substance.

Note: Lipopolysaccharide is one of the most potent pyrogens. If introduced into the blood stream, as little as 5 endotoxin units (1 ng) per kilogram body weight causes fever in rabbits and humans.

Regarding Dr. Favero's proposed definitions for disinfecton, high level disinfection, and low level disinfection, Ms. Annis pointed out that the USDA and FDA use the term "sanitize." Dr. Easterling invited her to provide commentary on the use of this term.

Quality Control. As noted above, in response to Mr. Kaufman's comment the definition was changed by replacing the word "verification" with the word "determination".

14. Reference Documents. It was agreed to consult Dr. Pizziconi as to whether the reference to SAX should be retained and, if so, how it should be completed.

Appendix A - Rationale

A9.3.2 Ultrafiltration. As a consequence of earlier discussion, the final paragraph of this portion of the rationale was deleted.

A9.4 Sterilization/Disinfection. The subcommittee considered Dr. Favero's objection to the third option for preparing chemical germicides for disinfection and sterilization and for rinsing dialyzers. It was noted that this option had been added at the recommendation of Dr. Pizziconi, but that Dr. Pizzinconi had presented no data to support it. It was agreed that under this option the potential for colonization exists. Following discussion, it was decided to modify this portion of the rationale to state that a third option had been suggested and to present Dr. Favero's reasons for rejecting it.

(Secretary's Note: Other changes have been made in the rationale, as mentioned above in the discussion of the corresponding sections of the main body of the document.)

Other Appendices.

Dr. Easterling pointed out that four additional appendices had been contemplated, as listed in the table of contents, but had yet to be prepared. Subcommittee members were asked to consider whether sample forms should be included as intended in the proposed Appendix C. With respect to proposed Appendix D on Kinetics of Sterilant Function, Dr. Gotch was asked to provide a how-to guideline. For Appendix E on Test Methodologies, Dr. Easterling suggested that sections of the Standard for First Use Hemodialyzers relative to clearance could be included and that Dr. Deane's material from the NIH report could also be useful. Subcommitte members were invited to offer tests to be included in this appendix. With respect to proposed Appendix F on Environmental Safety Regulations, it was decided this need not be completed, but was better handled by including appropriate references in the list of reference documents. (Secretary's Note: The chair has deleted these proposed appendices in the interest of timely development of the recommended practice. These issues may be addressed in a technical information report and/or through educational conferences.)

3. Plans for further development of recommended practice. Dr. Easterling observed that receipt of manuscripts from the November conference would facilitate further work on the draft document. It was agreed that the next meeting of the subcommittee be held in conjuction with ASAIO in Atlanta in early May 1985. There was also general agreement that, if the document were sufficiently complete, a subcommittee ballot should be conducted prior to the Atlanta meeting. It was in any case contemplated that following the Atlanta meeting the document could be prepared for ballot. (Secretary's Note: The next subcommittee meeting has been scheduled for 30 April 1985 in Atlanta.)

Adjournment. The meeting adjourned at approximately 5:00 p.m.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

DEC 31 1984

Mr. Perry S. Ecksel
Regional Coordinator
Kidney Patients Association
8400 Bustleton Avenue
Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Ecksel:

I am responding to your letter of October 30, 1984, to Secretary Heckler concerning the reuse of hemodialyzers.

As a physician, I can assure you that your question concerning a patient's right to demand what you describe as "a sterile treatment" in lieu of reprocessed equipment ". . . without the threat of reprisals" relates to the physician-patient relationship and is beyond the scope of the legal authority of the Food and Drug Administration or the Department of Health and Human Services. Prior consent, whether involving reuse of hemodialyzers or any other procedure, must be arrived at between the physician and the patient, and this is not an area in which FDA or HHS should properly be involved.

As you know, physicians and patients may differ--and even some physicians may differ among themselves--as to whether specific consent for using reprocessed hemodialyzers is required. It is a fact that the majority of dialysis facilities reprocess hemodialyzers, lending support to the premise that multiple use of hemodialyzers can now be considered standard medical practice. With this premise in mind, those who do not agree with obtaining formal consent from patients for multiple use of hemodialyzers argue that specific consent is not required for other aspects of dialysis therapy.

If there are physicians who believe that they have the right to refuse treatment to patients who do not consent to reuse of dialyzers, as your letter asserts, then I would hope the matter could be resolved between patient organizations such as yours, the National Kidney Foundation, or the National Association of Patients on Hemodialysis and Transportation, and individual physicians or physician organizations.

To ensure that physicians are aware of state-of-the-art procedures for the safe reuse of hemodialyzers, FDA is working with the Association for the Advancement for Medical Instrumentation to develop a recommended practice for reuse. FDA is also working with several State health departments to obtain data on hemodialyzer equipment, including reuse of dialyzers, and will study these data closely to determine possible future actions within the scope of its authority. Such actions are likely to include developing educational programs to inform both professionals and patients fully about the benefits and problems of dialysis treatment in general and reuse in particular.

In closing, let me emphasize that surely, for the majority of dialysis patients, an honest and trusting relationship with the physician providing treatment should be a guarantee of quality treatment whether reuse is practiced or not. I hope that you will be able to resolve the concerns you have about some of these patients through frank discussions between your organization and the appropriate physicians or physician organizations.

Sincerely yours,

James F. Dickson /for

Acting Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

0204

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March 5, 1985

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ADMIN. SIG. DUE 4/3

Dr. Carolyne K. Davis, Administrator
Health Care Financing Administration
200 Independence Avenue, S.W.
Washington, D. C. 20201

Dear Dr. Davis:

Over the last several years the Subcommittee on Health has heard many concerns about the practice of reusing disposable (labeled for one time use only) artifical kidney dialyzers (hemodialyzers).

As you know, the medicare program pays for more than 90 percent of the renal dialysis services provided in the United States. In 1982, the Congress approved legislation that provided for a new incentive reimbursement system for outpatient renal dialysis services provided to medicare beneficiaries. This prospective payment system provided strong incentives for cost containment. Partly in response to this legislation, I understand over 50 percent of the dialysis facilities now engage in the practice of reusing disposable dialyzers.

Needless to say, many beneficiaries are concerned about the health implications of reusing devices that are labled for one time use only. Many beneficaries say that they are being asked, and sometimes forced, to reuse.

The preponderence of medical evidence seems generally to indicate that reuse of hemodialyzers does not expose the patient to serious adverse health risks. I am concerned, however, that there are currently no generally accepted guidelines or regulations defining standards for reuse of hemodialyzers. As the medicare program is such a major purchaser of renal dialysis services and supplies, it seems to me that we in the Congress have a responsibility to examine this issue.

I have written to Dr. Young at the Food and Drug Administration asking for his views on this situation. I would like you to inform me if you feel there is a problem in this area and whether the medicare program, perhaps as a condition of payment, should require that each renal dialysis facility have, and follow, a written protocol on cleaning and reusing disposable dialyzers.

Dr. Carolyne K. Davis
March 5, 1985
Page Two

I would also like your views on the concern expressed by some medicare beneficiaries that they are being required to reuse against their will. Please comment on the appropriateness of, and any difficulties associated with, mandating an informed consent arrangement between the facility/physician and the beneficiary who is being asked to reuse.

This issue is very important to many medicare beneficiaries and I hope that you will respond to this letter at your very earliest convenience.

Sincerely,

Pete Stark

Fortney H. (Pete) Stark
Chairman

FHS/jp

cc: Frank E. Young, M.D.
Commissioner
Food and Drug Administration

FORTNEY H. (PETE) STARK, CALIFORNIA, CHAIRMAN
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COMMITTEE ON WAYS AND MEANS
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, DC 20515

SUBCOMMITTEE ON HEALTH

DAN ROSTENKOWSKI, ILLINOIS, CHAIRMAN
COMMITTEE ON WAYS AND MEANS

JOSEPH K. DOWLEY, CHIEF COUNSEL
A.L. SINGLETON, MINORITY CHIEF OF STAFF

PAUL C. RETTIG, SUBCOMMITTEE STAFF DIRECTOR

March 5, 1985

Frank E. Young, M.D.
Commissioner
Food and Drug Administration
Dept. of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Young:

Over the last several years the Subcommittee on Health heard many concerns on the practice of reusing disposable (labeled for one time use only) artifical kidney dialyzers (hemodialyzers).

As you know, the medicare program pays for more than 90 percent of the renal dialysis services provided in the United States. In 1982, the Congress approved legislation that provided for a new incentive reimbursement system for outpatient renal dialysis services provided to medicare beneficiaries. This prospective payment system provided strong incentives for cost containment. Partly in response to this legislation, I understand over 50 percent of the dialysis facilities now engage in the practice of reusing disposable hemodialyzers.

Needless to say, many beneficiaries are concerned about the health implications of reusing devices that are labeled for one time use only. Many beneficiaries say that they are being asked, and sometimes forced, to reuse.

The preponderance of evidence seems to indicate that reuse of hemodialyzers does not expose the patient to serious adverse health risks. I am concerned, however, that there are currently no generally accepted guidelines or regulations defining standards for reuse of hemodialyzers. As a hemodialyzer is in fact a medical device, is this not an area in which the Food and Drug Adminstration (FDA) should be involved in?

I am asking you to inform me as to what role you see the FDA playing in the hemodialyzer reuse issue. Do you believe that there is a need for regulations governing reuse, or at least guidelines, if one assumes that hemodialyzers will continue to be reused as they have in the past?

I understand that the FDA has a heavy burden of responsibility in the medical devices area. Nonetheless, I am concerned that very little attention appears to have been given by the FDA to the practice of dialyzer reuse. Considering the size of the medicare end stage renal disease population, it occurs to me that reviewing the practice of hemodialyzer reuse should have a high priority for the FDA.

Thank you for your attention to this important matter. I think this issue will be with us for quite a while and I look forward to receiving a report on the actions FDA has taken on this issue and any recommendations you may have.

Sincerely,

Fortney H. (Pete) Stark
Chairman

FHS/jp

cc: Dr. Carolyne K. Davis

The Honorable Fortney H. (Pete) Stark
Chairman, Subcommitee on Health
Committee on Ways and Means
House of Representatives
Washington, D.C. 20515

MAY 0 3 1985

Dear Mr. Stark:

I write to respond to your letter of March 5, 1985 in which you inquired about the reuse of hemodialyzers in the treatment of End Stage Renal Disease and the Food and Drug Administration's role in this matter.

I hope that the enclosed report with attachments provides you with the information you need. My staff and I would be happy to meet with you, should you wish to discuss this matter in more detail.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

MARY GRIS
MI-G

DRAF

Honorable Fortney H. Stark
Chairman
Subcommittee on Health
Committee on Ways and Means
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Stark:

This is in response to your letter of March 5, 1985, in which you inquired about the reuse of hemodialyzers in the treatment of End Stage Renal Disease (ESRD), and the Food and Drug Administration's role in this matter.

The Food and Drug Administration (FDA) has been aware of and concerned about reuse of hemodialyzers for several years. Staff from the Center for Devices and Radiological Health (CDRH) are actively working with outside organizations towards insuring that reuse as practiced in the treatment of ESRD is safe and effective.

The absence of any regulatory initiative does not signify a disinterest on the part of FDA on the reuse issue. On the contrary, there have been many actions taken by FDA, especially with respect to our association with these outside organizations where FDA has made, I believe, significant contributions. These initiatives have been directed towards the safety and effectiveness of reused hemodialyzers which have made the need for regulatory action unnecessary.

The following examples are highlights of FDA's actions showing that we recognized the potential problems and benefits associated with reuse and took the necessary steps to provide technical, moral, and financial support to the dialysis community in this matter:

1. June 1980. CDRH (formerly the Bureau of Medical Devices) published a report entitled, "Investigation of the Risks and Hazards Associated with Hemodialysis Devices."[1] Chapter XII is devoted to the issue of Reuse of Hemodialyzers. The chapter describes both the risks and benefits associated with reuse of hemodialyzers, but recommended that no regulatory action, such as mandatory standards, be undertaken until the ongoing studies being sponsored by the National Institutes of Health (NIH), establishing appropriate criteria for reuse of hemodialyzers, were completed.

2. July 1981 FDA issued a revised compliance policy guide No. 7124.16[2] on the reuse of disposable medical devices. That guide places the responsibility for reuse on the institution or practitioner who reuses a disposable medical device.

3. March 1982 FDA in cooperation with the Health Care Financing Administration, the Veterans Administration, The National Institutes

(AAMI) to prepare a "Recommended Practice for the Reuse of Hemodialyzers". The third draft[4] of that document is now being balloted within AAMI.

This document, which is addressed to the physician responsible for the reprocessing program in his or her facility, is being developed by recognized experts from the medical, governmental, and industrial communities. The guideline provides essential elements of good operating practice for reprocessing hemodialyzers to help assure product safety and effectiveness.

5. August 1983 CDRH established a committee on reuse of medical devices to serve as a focal point for planning the Center's programs and policies concerning the reuse of medical devices. The committee is currently reviewing FDA regulatory authority with respect to reuse, and it intends to initiate a public rule making proceeding defining FDA's policy with respect to reuse.

of Health, the Center for Disease Control, and numerous private organizations involved with kidney disease cosponsored a workshop on the reuse of consumables used in Hemodialysis.[3] The findings of the workshop indicated that "dialysis using reprocessed consumables is clearly a widely accepted modification of standard treatment, not research." However, since the practice was still in an evolutionary stage the attendees of the workshop believed that it merited careful monitoring and investigation under appropriate protocols designed to improve the safety and efficiency of the practice. The attendees also confirmed their belief that reuse of consumable was a facet of medical practice subject to the blame, responsibilities, potential liabilities, and standards as the overall practice of medicine.

4. May 1983 Staff of CDRH joined with physicians, engineers and manufacturers under the auspices of the Association for the Advancement of Medical Instrumentation

6.	March 1984	FDA co-sponsored, with the Institute for Health Policy Analysis (IHPA) at Georgetown University, an international conference on "The Reuse of Disposable Medical Devices in the 1980's".[6] The purpose of the conference was to consider all aspects of the reuse question, including, safety, effectiveness, cost, ethical, legal, and regulatory implications. Results of that conference indicated that reuse of medical devices appears to be widespread but is poorly characterized and, that hemodialyzers are the only device for which there is substantial documentation of the risks and benefits of reuse. The conference report also recommended that IHPA continue its work to facilitate further discussion of the issues.
7.	October 1984	CDRH initiated a contract with four State health departments to review the whole system of dialysis treatment in their States, including hardware, labeling, reuse, and procedures of operation. Under this contract, the States will assist the CDRH in identifying and setting priorities for problems in

dialysis which may require regulatory action or, if user related, development of educational or training programs to prevent future problems related to the equipment.

8. March 1985 — Staff of CDRH is continuing to work with IHPA as a co-sponsor to develop a conference on the legal and public policy aspects of reuse. The conference, expected to be held in the fall of 1985, will provide FDA with information which can be used in developing its policy with respect to reuse.

Although the driving force behind the reuse of hemodialyzers is primarily economic, the increase in the number of patients treated with reused hemodialyzers is, to some extent, due to the publication of data which supports the safety and efficacy of the reuse of the dialyzers. Data to this effect was published in a final report to the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases.[6] The author, Dr. Norman Deane, states in his conclusions: "Utilization of specified procedures (for reuse) with suitable process and quality control, will result in a reprocessed hollow fiber hemodialyzer equivalent in terms of function, cleanliness, and sterility to a new hollow fiber hemodialyzer".

All persons who are knowledgeable with respect to the reuse of hemodialyzers agree that the single most important determinant of the final outcome of reprocessing is the specific procedure used for reprocessing the dialyzers. The National Kidney Foundation (NKF) also recognizes that the reuse of Hemodialyzers can be safe and effective if adequate reprocessing is practiced and has issued revised standards for the reuse of hemodialyzers.[7]

We realize, however, that the safety and efficacy of reuse is still a subject of some discussion. While there are some reports in the literature regarding potential adverse affects of reuse, there are many others, such as the Deane report, that indicate that dialyzer reuse is not only a safe and effective practice with minimal patient complications, but may, in fact, present fewer health complications than single use.

It should be noted that single use of dialyzers does not always insure the absence of patient symptoms. It has been documented[8] that severe anaphylactic-like reactions related to the first use of dialyzers (first use syndrome) occasionally do occur and may be life threatening. CDRH was concerned enough about this problem to issue an alert to physicians describing the syndrome and suggesting procedures to be followed to reduce the risk to the patent (copy enclosed).

We have had correspondence with patient groups such as the Kidney Patients Association and are, therefore, aware of patients' concerns about the quality of care they receive when using reprocessed hemodialyzers. FDA regards the decision of whether or not to reuse a hemodialyzer as one between the physician and the patient and FDA will not interfere with the process. The AAMI draft guideline on the reuse of hemodialyzers also addresses the issue in a section on "Patient Considerations". A list of specific indications and contraindications are presented as is a discussion on informed consent and on the patient/physician relationship. FDA believes that for the majority of dialysis patients, an open relationship between the physician and the patient is the best guarantee of quality treatment whether reuse is practiced or not.

With respect to our regulatory actions; FDA regulates the manufacturer and/or distributor of medical devices. We do not regulate the user (i.e., the dialysis center, the physician, nursing staff, or patient). Our primary objective is to insure that the device, as manufactured, is safe and effective. Our policy, at the present time with respect to a person or institution who reuses a "single use" device, as outlined in our Compliance Policy Guide, 7124.16[1], is to place the responsibility for reuse on the user who should be able to demonstrate that the device can be adequately cleaned and sterilized; that the physical characteristics are not adversely affected; and that the device remain safe and effective for its intended use.

Beyond our specific regulatory responsibilities the CDRH also has public health concerns about the safety of medical devices. These concerns stem both from the broad aspects of the Public Health Service Act and from the role of labeling and education implicit in the Medical Device Amendments. To further these non-regulatory activities the Center has initiated programs which will develop data on hemodialyzer equipment, including the reuse of dialyzers. The data will form the basis of future activities, if necessary, such as the development of educational programs which can inform both professionals and patients about the benefits and problems inherent in the process of dialysis treatment in general and reuse in particular.

In view of FDA's constant involvement in the technical aspects of reusing hemodialyzers, and our knowledge of the issues involved, we do not believe that further regulation is necessary or warranted at this time. We believe FDA already has legal authority to mandate appropriate controls regarding reused medical devices if it should become necessary.

I hope this letter provides you with the information you need.

My staff and I would be happy to meet with you, should you wish to discuss this matter in more detail.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food
and Drugs

Enclosures

[1] "Investigation of the Risks and Hazards Associated with Hemodialysis Devices", NTIA PB80215403, 5285 Port Royal Road, Springfield, Virginia 22161.

[2] FDA Compliance Policy Guide 7124.16 dated July 1, 1981.

[3] Report of National Workshop on reuse of Consumables in Hemodialysis March 1-2, 1982
Washington, D.C.
Copies, if still available, may be obtained from:
Dr. John H. Sadler, M.D.
Program Chairman
Associate Professor of Medicine
Head, Division of Nephrology
University of Maryland School of Medicine
Baltimore, Maryland

[4] Recommended Practice for Reuse of Hemodialyzers (March 1985 Revision) AAMI ROH-D-3/85.

AAMI 1901 N. Fort Myer Drive
Arlington, VA 22209

[5] Conference Proceedings, International Conference on the Reuse of Disposable Medical Devices in the 1980's, March 29-30, 1984.

Institute for Health Policy Analysis
Georgetown University Medical Center
2233 Wisconsin Ave., N.W.
Suite 324
Washington, D.C. 20007

[6] N. Deane and J.A. Bemis, "Multiple Use of Hemodialyzers. A Report to the National Institute of Arthritis, Diabetes and Digestive and Kidney Disease", NTIA PB80215403, 5285 Port Royal Road, Springfield, Virginia 22161. 1981

[7] "National Kidney Foundation Revised Standards for Reuse of Hemodialyzers," NAPHT NEWS, May 1984.

[8] "Artifical Organs, Volume 8 #3, August 1984"

Drafted:LKobren:al:4/3/85:jts:4/4/85 l-stark in LNK
reviewed:CKShowalter

Drafted:LKobren:al:4/3/85:jts:4/4/85 l-stark in LNK
reviewed:CKShowalter

Initialed:JMorrison(for J.Arcarese):4/9/85 4/22
Initialed:JShowalter:4/15/85
EDITED ~~Concurrence by Phone~~:FVillarroel:4/18/85
Initialed:JSBenson:4/18/85
Initialed:JCVillforth:4/18/85
revised:LKobren:4/19/85:jts
revised:JArcarese:4/22/85

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

November 30, 1983

Medical Director
Dialysis Services

Dear Doctor:

Since 1982, the Food and Drug Administration (FDA) has been monitoring reports concerning severe hypersensitivity reactions with new dialyzers (also called first-use syndrome) that occur in end-stage renal disease patients. These anaphylactic-like reactions occur in patients within the first few minutes of a dialysis treatment and require that the dialysis procedure be stopped immediately. Manifestations include nausea, malaise, weakness, a sensation of burning or heat throughout the body, profuse perspiration, respiratory distress and in some instances hypotension and cardiopulmonary arrest. Although the frequency of occurrence of these severe reactions is low (3 to 4 reactions per 100,000 dialyzers sold in the U.S. during 1982), they may be life threatening and require that resuscitative measures be initiated.

Experts at the "Symposium on Hypersensitivity in Hemodialysis" held in Louisville, Kentucky, on July 21 and 22, 1983, discussed possible causes of this reaction. One potential cause is traces of residual material from the manufacturing process in the dialyzer blood path. The discussants believed that water is the most effective flushing agent known for removing any residues, and emphasized the importance that the user strictly adhere to the manufacturer's rinsing and priming recommendations, as this procedure serves not only to remove air but also to reduce any trace amounts of residual material that might be left from the manufacturing process. They also noted that residual material might not be completely removed by the rinsing procedure performed by manufacturers, who cannot use water for rinsing if the dialyzer is to be sold dry. (The proceedings of this workshop will be published in Artificial Organs.)

FDA has examined case reports and found that about sixty percent of the severe hypersensitivity reactions reported in 1982 occurred with dialyzers that were rinsed using procedures other than those recommended by the manufacturer.

In view of the above, it would seem reasonable to assume that improved rinsing of the dialyzer by the user should minimize the risk of a patient having a hypersensitivity reaction. Therefore, FDA recommends:

1) Strict adherence to the dialyzer rinsing and priming procedure given in the labeling of the device, as a minimum.

2) That all personnel concerned with dialyzer preparation be informed that if appropriate rinsing and priming procedures are not followed, susceptible patients may be at greater risk of having hypersensitivity reactions.

3) That all hypersensitivity reactions be fully and promptly reported to the dialyzer manufacturer.

If you have any questions, please contact Dr. Fernando Villarroel, Director, Division of Gastroenterology-Urology and General Use Devices at (301) 427-7750.

Sincerely,

Marlene E. Haffner, M.D., F.A.C.P.
Acting Director
Office of Health Affairs (HFK-200)
National Center for Devices
and Radiological Health

FORTNEY H. (PETE) STARK, CALIFORNIA, CHAIRMAN
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JUDD GREGG, NEW HAMPSHIRE

Ex Officio:
DAN ROSTENKOWSKI, ILLINOIS
JOHN J. DUNCAN, TENNESSEE

COMMITTEE ON WAYS AND MEANS
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, DC 20515

SUBCOMMITTEE ON HEALTH

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A.L. SINGLETON, MINORITY CHIEF OF STAFF

PAUL C. RETTIG, SUBCOMMITTEE STAFF DIRECTOR

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March 5, 1985

Frank E. Young, M.D.
Commissioner
Food and Drug Administration
Dept. of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Young:

Over the last several years the Subcommittee on Health heard many concerns on the practice of reusing disposable (labeled for one time use only) artifical kidney dialyzers (hemodialyzers).

As you know, the medicare program pays for more than 90 percent of the renal dialysis services provided in the United States. In 1982, the Congress approved legislation that provided for a new incentive reimbursement system for outpatient renal dialysis services provided to medicare beneficiaries. This prospective payment system provided strong incentives for cost containment. Partly in response to this legislation, I understand over 50 percent of the dialysis facilities now engage in the practice of reusing disposable hemodialyzers.

Needless to say, many beneficiaries are concerned about the health implications of reusing devices that are labeled for one time use only. Many beneficiaries say that they are being asked, and sometimes forced, to reuse.

The preponderance of evidence seems to indicate that reuse of hemodialyzers does not expose the patient to serious adverse health risks. I am concerned, however, that there are currently no generally accepted guidelines or regulations defining standards for reuse of hemodialyzers. As a hemodialyzer is in fact a medical device, is this not an area in which the Food and Drug Adminstration (FDA) should be involved in?

Frank E. Young, M.D.
March 5, 1985
Page Two

[illegible]

I am asking you to inform me as to what role you see the FDA playing in the hemodialyzer reuse issue. Do you believe that there is a need for regulations governing reuse, or at least guidelines, if one assumes that hemodialyzers will continue to be reused as they have in the past?

I understand that the FDA has a heavy burden of responsibility in the medical devices area. Nonetheless, I am concerned that very little attention appears to have been given by the FDA to the practice of dialyzer reuse. Considering the size of the medicare end stage renal disease population, it occurs to me that reviewing the practice of hemodialyzer reuse should have a high priority for the FDA.

Thank you for your attention to this important matter. I think this issue will be with us for quite a while and I look forward to receiving a report on the actions FDA has taken on this issue and any recommendations you may have.

Sincerely,

Pete Stark

Fortney H. (Pete) Stark
Chairman

FHS/jp

cc: Dr. Carolyne K. Davis

INTEROFFICE MEMORANDUM

@ REUSE PMS

Memo: [46146.3797108.OPSO]
Date: Fri 22-MAR-1985 10:32
From: OSR - Operations
Dept: OSR-OS
Tel: 301-443-4874

TO: Kobren, Lawrence (LNK)

Subject: Reuse Committee Minutes

Members Present
Jim Chantler, HFZ-323
Sally Hedrick, HFZ-250
Charlotte Silverman, HFZ-104
Norman Welford, HFZ-420
Donna Lanahan, HFZ-30
Fernando Villarroel, HFZ-420
Nancy Lowe-Clements, HFZ-84
Frank Morlock, HFZ-84

Date: March 14, 1985

Discussion

1. The chairman, Larry Kobren, reported that the Center FY-86 planning cycle was about to begin and requested Committee input regarding the reuse policy. On April 1, a "Go Away" meeting will kick-off the annual planning cycle and Committee issues are due by Monday, June 3.

2. Roger Schneider will moderate a session on the legal/technical issues of reuse at the annual Georgetown U Conference on Reuse. The Committee is to provide him with questions/issues. Dr. Skufca, Dr. Gordon, and Jim Chantler have already provided questions, and other committee members are encouraged to submit any comment as soon as possible.

3. A lengthy discussion was held on the draft outline of the Center Reuse Policy. Legal definitions of commerce (vs. profit), repair, reprocess, user manufacturer, etc. were discussed at length. Several. Committee members expressed the opinion that the reuse policy should retain FDA's broad authority to inspect "manufacturers" but provide exemptions for hospitals, clinicians, and physicians.

Next Meeting

April 10, 1:00-3:00 p.m. ,T-400.

Nancy Clements

FAVERO (AFF.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

April 8, 1985

Ms. Elizabeth A. Bridgman
Manager for Technical Development
Association for the Advancement of
Medical Instrumentation
Suite 602
1901 N. Ft. Myer Drive
Arlington, Virginia 22209-1699

RECEIVED APR 15 1985

Dear Ms. Bridgman:

Mr. Lee Bland and I have reviewed the March 1985 revision of "Recommended Practice for Reuse of Hemodialyzers" as well as the minutes of the December 1984 Subcommittee Meeting. I have enclosed our vote (affirmative with comments) and the following are our comments:

Section 5.1, Water Systems

The incident that occurred in Atlanta, Georgia where dialysis patients were accidentally exposed to formaldehyde solutions has nothing to do with reprocessing hemodialyzers. This center has three central proportioners and had just finished the process of disinfecting one of these central proportioners with formaldehyde. The proportioner containing formaldehyde did not have a back-flow protection device and formaldehyde flowed from this proportioner to the other two proportioners which were running. We do not believe that a center should be prevented from using water intended for preparing dialysis fluid for reprocessing dialyzers including water that is used to prepare the disinfectant solutions.

Section 9.2.2, Water Quality

I have enclosed an additional paper "Bacterial Endotoxin and New and Reused Hemodialyzers: a Potential Cause of Endotoxemia." This report contains data on the ability of endotoxin in water to adhere to the components of a dialyzer and it should be cited along with the other reference by Petersen, et al. We realize the subject of bacteriologic and endotoxin quality of water for reprocessing dialyzers is one for which there is not a complete consensus among the committee members. We believe that there should be some degree of quality control on this type of water. We have had various opinions presented to the committee. These range from no tests to tests for bacteria (no more than 200 bacteria per ml), endotoxin (less than one ng per ml) and tests such that the water meet the AAMI specifications for chemical contaminants for water used to prepare dialysis fluid. We do not believe that all tests are necessary, especially the chemical specifications. If one uses the AAMI bacteriologic standard for water used to prepare to dialysis fluid there is no guarantee that the organisms of greatest concern, the non-tuberculous mycobacteria, will also be reduced since the current culture methods do not allow for their detection and there is no feasible quantitative standard. Nonetheless one might assume control procedures directed to the gram negative water bacteria might also reduce the number of non-tuberculous mycobacteria in water.

The use of the endotoxin guidelines for water used to prepare the disinfection solutions has a much more realistic scientific base. There have been reports to the CDC where water used for this purpose which contained endotoxin subsequently resulted in pyrogenic reactions in the patient. We have no idea of the frequency of this type of episode among all of the centers who reuse dialyzers in the United States. However, the risk appears to be real. Further, the value of one ng per ml of water is based on the FDA regulation for endotoxin contents of medical devices that see blood (.1 ng per ml) and appropriation extrapolations to the average size of a dialyzer. In our experience the LAL test, if done properly, is a relatively precise test. Further, it is relatively inexpensive, and if a choice were to be made between doing an endotoxin test versus a bacteriologic assay on water meant for reprocessing we would favor using the endotoxin test (i.e. for water used for preparing disinfectant solutions).

Section 9.4.1.1, Germicide

We would suggest the following modifications: with the sentence "If formaldehyde is used as the sole disinfecting agent the Centers for Disease Control recommends a concentration of 4% in both the blood and dialysis compartments with a minimum contact time of 24 hours at a temperature of 10-20°C (50 - 70°F.)" Comment - we do not believe that there should be any indication of shorter contact times if "adequate" disinfection can be demonstrated. What is adequate disinfection?

"When other disinfectants are used instructions by the manufacturer of the germicide should be followed. Comment - the following phrase should be deleted "If the product is recommended for reprocessing or appropriate testing done to demonstrate adequate disinfection".

9.4.1.1, Non-tuberculous Mycobacterial Infections in Dialysis Patients.

In addition to the major outbreak of infections in Louisiana there have been two instances where non-tuberculous mycobacterial infections in dialysis patients reported to CDC. In one instance, microbiologic assays incriminated the water supply as the source of the mycobacteria and determined 2% aqueous formaldehyde to be an inadequate disinfection procedure. In our large survey of 115 dialysis centers, the data for which are still being analyzed, there has been a total of 6 non-tuberculous mycobacterial infections reported.

We continue to believe strongly that 2% formaldehyde, which barely qualifies as a disinfection procedure and should probably be classified as a sanitization procedure, is inadequate for reprocessing of a medical device, the hemodialyzer, that sees the patient's vascular system. It is neither a sterilization nor high-level disinfection procedure. The probability that viable microorganisms will be contained in the dialyzer as the result of using this inadequate procedure is high. This may not result in clinical infection but in our view the use of such a device cannot be justified. Non-tuberculous mycobacteria are commonly found in water and results of our survey of 115 dialysis centers across the United States show that over 80% of these centers had mycobacteria in water associated with the center. These organisms cannot be ignored.

How many outbreaks of non-tuberculous mycobacteria among dialysis patients are needed to indicate that 2% formaldehyde is an inadequate proceddure for disinfecting hemodialyzers?

Section 9.4.2

Although 1% sodium hypochlorite (10,000 ppm) is an adequate disinfecting solution for the exterior hemodialyzers, 0.05 to 0.1% (500 to 1000 ppm) is also adequate.

Both Lee and I plan on attending the Subcommittee Meeting on April 30 and will be looking forward to seeing you.

Sincerely yours,

Martin S. Favero, Ph.D.
Chief, Nosocomial Infections
  Laboratory Branch
Hospital Infections Program
Center for Infectious Diseases

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing Administration

The Administrator
Washington, D.C. 20201

OEP

APR 10 1985

due 3/26/85
Stark

The Honorable Fortney H. (Pete) Stark
House of Representatives
Washington, D.C. 20515

Dear Mr. Stark:

This is in response to your inquiry about the absence of standards for reusing disposable hemodialyzers. I am acutely aware of the controversy surrounding this issue. As you indicate, much data has been published which supports the safety and efficacy of reuse. At the present time, I believe the question of reuse is a medical practice issue which, in the absence of specific guidelines from the Food and Drug Administration (FDA), should be decided by the patient's physician.

A recent study conducted by the Association for the Advancement of Medical Instrumentation addresses such issues as reprocessing material, hemodialyzer labeling, reprocessing and storage procedures and disposal of rejected dialyzers. The FDA is currently examining this study. When we receive the FDA comments, we will consider what steps, if any, should be taken by the Health Care Financing Administration (HCFA), including the related question of physician/patient informed consent arrangements.

I should point out that the State surveyors of Medicare facilities that reuse hemodialyzers do check to determine whether facilities have a written policy covering the number of times dialyzers can be safely reused, including procedures for the cleaning, sterilizing and storage of dialyzers. HCFA does not, at present, provide specific standards to facilities, however.

I appreciate your interest in this issue, which is of concern to many Medicare beneficiaries and to HCFA as the primary payor for dialysis services.

Sincerely yours,

Carolyne K. Davis, Ph.D.

Please see R600 - policy OPSO - Mulick
RANO - Kathy Shanahan
[redacted]
See Attached Memo

REUSE COMMITTEE MINUTES

Members Present

✓ Larry Kobren, HFZ-240
✓ Sally Hedrick, HFZ-250
✓ Frank Morlock, HFZ-83
✓ Charlotte Silverman, HFZ-104
✓ Nancy Clements, HFZ-84

James Chantler, HFZ-323
✓ Evelyn Gordon HFZ-70
✓ Kathy Shanahan, HFZ-323
✓ Fernando Villarroel, HFZ-420
✓ Norma Welford, HFZ-420
✓ ~~Kim~~ Scuf Ca, HFZ-135

Date: April 24, 1985, 2:00 p.m., T-416

The chairperson, Larry Kobren, called the meeting to order and distributed copies of the first draft the Health Spa article on FDA's position on reuse. He also circulated copies of the Center's response to Congressman Stark's letter inquiring whether FDA needed additional legislation to regulate hemodialysis devices. Copies of an English article on the reuse of plastic syringes were also distributed.

Issues for the PHS briefing were the primary focus of the meeting. It was agreed to present the need for a comprehensive reuse policy as the major issue and the revision of the compliance guides as a subsection. The need to publicize FDA's policy on reuse is also to be part of the briefing.

Dr. Silverman stressed the need to change the word "objectionable" in Compliance Guide 7424.12. Dr. Gordon and others recommended that the compliance guideline be neutral rather than positive or negative as presently stated. The committee agreed to begin filling out Frank's matrix, so that the different types of reused devices could be addressed.

Action Item: Refine issues for June 3 submission deadline; Frank and Nancy help Larry with the writing.

Next Meeting: Friday, May 10, 2:00 p.m., T-416. Wednesday, May 22, 1:30

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing
Administration

Regional Office VI
1200 Main Tower Building
Dallas, Texas 75202

April 26, 1985

Our Reference: SC-20
SC-160

REGIONAL HEALTH STANDARDS AND QUALITY LETTER NO. 85-13

To: All State Survey Agencies (Action)
All Title XIX Single State Agencies (Information)

Subject: Reuse of Single-Use and Disposable Medical Equipment in ESRD Facilities

The reuse of single-use and disposable medical equipment is becoming a very common occurrence, particularly in ESRD facilities. The medical efficacy and safety of reuse is the subject of great debate and widely differing opinions. When reuse is encountered, the surveyor must verify that the facility has policies and procedures governing reuse. The reuse of single-use items in itself should not be considered a deficiency unless prohibited by facility policy. The reuse of disposable devices without effective policies and procedures governing their reprocessing and reuse is an extremely serious deficiency which may represent a hazard to patient health and safety.

If you have any questions about this letter or our position in this matter, please contact your State liaison person.

Kenneth C. Schneider

Kenneth C. Schneider, M.D.
Associate Regional Administrator
for Health Standards and Quality

MINUTES

of the

AAMI HEMODIALYZER REUSE SUBCOMMITTEE

30 April 1985
Atlanta, GA

1. Opening of the meeting. The meeting was called to order at 10:15 a.m. by Ronald E. Easterling, M.D., the medical cochairman. It was reported that the industry cochairman, Albert E. Jarvis, Ph.D., had conveyed his regrets at being unable to attend due to other commitments. Elizabeth Bridgman of AAMI staff served as recording secretary.

Committee and Subcommittee Members/Alternates Present

Rose Annis, Alcide Corp.
Lee Bland, Centers for Disease Control
James Dugan, CD Medical
Ronald E. Easterling, M.D., Hurley Medical Center
Martin Favero, Ph.D., Centers for Disease Control
L.J. Fischbach, Renal Systems
Lois Foxen, R.N., St. Joseph Hospital Renal Center
Marilyn Gould, Ph.D., Associates of Cape Cod, Inc.
Lawrence Kobren, CDRH/FDA
Nathan Levin, M.D., Henry Ford Hospital
Joseph H. Miller, M.D., Wadsworth VA Medical Center
Vincent Pizziconi, Ph.D., Arizona State University
Roberta Thorpe Potaki, National Medical Care
Martin Roberts, Ph.D., Organon Teknika
John H. Sadler, M.D., University of Maryland
Fernando Villarroel, Ph.D., CDRH/FDA

Guests Present

Elizabeth A. Bridgman, AAMI
Tommy Brown, CD Medical
Hugh Dodson, Continental Water Systems Corp.
Gary Warns, Cobe Laboratories
Bob Waters, CD Medical

2. Approval of minutes. The minutes of the 7 December 1984 subcommittee meeting were approved as distributed.

3. Resolution of comments on draft recommended practice for reuse of hemodialyzers. Dr. Easterling noted that the results of the March 1985 ballot of the Renal Disease and Detoxification Committee and the Hemodialyzer Reuse Subcommittee had been distributed prior to the meeting. Ms. Bridgman reported that the correct, updated tally of votes was as follows: 56 ballots were distributed, 36 were returned; of the 36

returned, 29 were affirmative (12 with comments), 3 were negative, and there were 4 abstentions. The subcommittee then reviewed the compilation of comments.

(Secretary's Note: Attachment 1 contains the final voting results, the compilation of comments, and proposed responses to comments developed at the subcommittee meeting. Where significant additional discussion occurred, this is recorded below.)

Water quality for reprocessing--Sections 9.2.2 and 9.4.1.2. There was considerable discussion of the quality, treatment, and testing of water used for rinsing and for preparing germicide. A fundamental question was whether to rely on the LAL test for endotoxin, since experience with this test is relatively limited; most practitioners are accustomed to relying on bacterial colony count, the established criterion for water used in preparing dialysate. The point was made that water meeting the limit of 200 colonies per ml could still contain significant amounts of endotoxin. Dr. Favero noted that a clear distinction should be made between rinse water (9.2.2) and water used to prepare germicide (9.4.1.2): there is no point in bacteriologic testing of water used for rinsing because it spends little time in contact with the membrane, while water used to prepare germicide should undergo bacteriologic testing because the membrane is exposed to it for extended periods of time. Based on these discussions it was agreed to remove the requirement for bacteriologic testing from section 9.2.2 except for a reference to 9.4.1.2 when the water used to rinse the hemodialyzer is also used to prepare the germicide (as is the case in certain reprocessing machines). Furthermore, since the purpose of filtering rinse water is to remove particulates which may damage the dialyzer, it was concluded that a nominal 5 micron filter would suffice (the reference to reverse osmosis water will be moved to the rationale). There was general agreement that ordinary potable water was of sufficient quality to be used for rinsing, and the rationale should explain that there is no evidence for high quality water being required for rinsing from the point of view of exposing the patient to chemical contaminants. The committee noted that there is evidence that the use of high quality water for reprocessing hemodialyzers increases the number of uses already stated in the rationale. These observations are presented in section A.9.2. Consequently, section 9.2.2 was revised to read as follows:

> 9.2.2 Rinsing/cleaning should be done with a fluid or fluids prepared with potable water that result in the dialyzer meeting the specification of 9.3. If the rinsing fluid is tap water or a solution made with tap water, the water should be filtered through a nominal 5-micron filter. If the water is also used to dilute the germicide, it shall meet the requirements of 9.4.1.2.

With regard to the question of LAL testing, Dr. Favero commented that the recommended colony count of 200 per ml is taken from the AAMI standard for water used for dialysis and that this limit is an estimate of what is required to prevent the final dialysate solution from having a colony count in excess of 2000 per ml (higher levels are associated with pyrogenic reactions during dialysis). Additionally, he pointed out that in the case of reprocessing hemodialyzers, that LAL levels rather than bacterial colony counts have been used to define the bacterial contamination levels above which pyrogenic reactions may occur. Consequently, if forced to make a choice, he would recommend LAL testing over bacterial colony counts.

In light of the above discussion and the proposed response to Dr. Gould's general comments (see Attachment 1), it was agreed to modify section 9.4.1.2 to offer either bacterial colony count (200 colonies per ml) or endotoxin level (1 ng per ml) as alternatives for establishing diluent water quality. Section 9.4.1.2 therefore was modified to read as follows:

> 9.4.1.2 Diluent. The water used to prepare the germicide solution should have a bacterial colony count of less than 200 per ml and/or a bacterial lipopolysaccharide concentration of less than 1 ng/ml as measured by the Limulus amebocyte lysate assay.

The recommendation that diluent be of the same chemicl quality as dialysate was deleted, since there is not a consensus on this issue. (See discussion of quality of rinse water above - A9.4.1.2 references A9.2. on this matter.)

9.3.1 Performance Measurements/Clearance. (In addition to the following discussion, see the compilation of comments and response for section 9.3.1.3 in Attachment 1.) Dr. Pizziconi stated that the reason for his negative vote (which had not been accompanied by written comments) was explained in commentary he had provided to the subcommittee in August 1984 and in his presentation at the November 1984 conference. See Attachment 2 for Dr. Pizziconi's August 1984 comments.) His primary objection was the reliance on fiber bundle volume testing without recognizing its inherent limitations. While FBV is satisfactory for measuring clearance of smaller molecules, he said, it is unsatisfactory for larger molecules because of the presence of a protein film. He stated that ultrafiltration rate may be preferable in some cases, and suggested that perhaps the best approach would be to use both FBV and UFR tests. He added that UFR was the first test approved by the FDA, and is widely used as a primary test for clearance.

Dr. Levin observed that large molecule clearance has not been shown to be of clinical significance within the range affected by reprocessing hemodialyzers. Dr. Sadler pointed out that FBV is the customary test, that a consensus exists about its use, while there is no consensus concerning UFR. Dr. Pizziconi reiterated his point that FBV does not measure protein film, and this affects large molecule transport; he felt that the document should not recommend FBV without recognizing its limitations.

Dr. Easterling noted that any substantive change in the document would require a reballot. He also pointed out that neither Dr. Pizziconi nor Dr. Gotch had yet submitted manuscripts from the November conference, which would provide a basis for comparing the cases for FBV and UFR. No resolution of this issue was reached, and Dr. Easterling stated that he would discuss it further with Dr. Gotch and Dr. Pizziconi following the meeting.

(Secretary's Note: The compilation of comments, Attachment 1, now includes one additional comment from a public reviewer, Etty Dolin, which was inadvertently omitted from the material previously distributed. This comment concerns section 10.3, and the proposed response was developed by Dr. Easterling.)

4. Further development of the draft recommended practice. The subcommittee agreed that the document should proceed to AAMI public review after being revised as agreed at this meeting. While the introduction of the endotoxin test as an alternative to bacterial colony count in section 9.4.1.2 was not considered a substantive change which would require reballot, it was agreed that this change should be highlighted in the cover memo for these minutes. Assuming that the ultimate resolution of Dr. Pizziconi's concerns did not result in substantive change, no reballot would be required.

Adjournment. The meeting adjourned at approximately 6:00 p.m.

ATTACHMENT 1

RECOMMENDED PRACTICE FOR REUSE OF HEMODIALYZERS
(March 1985 Revision)

A committee and subcommittee ballot on the Draft Recommended Practice for Reuse of Hemodialyzers commenced on 8 March 1985, with an initial deadline for response of 19 April 1985. This was subsequently extended to 29 April 1985.

The ballot yielded the following results: Of 56 letter ballots distributed, 37 were returned. Of the 37 returned 30 were affirmative (11 with comments), 3 were negative and there were 4 abstentions.

The votes cast by members and alternates of the Hemodialyzer Reuse Subcommittee and Renal Disease and Detoxification Committee are listed below. This summary is followed by a compilation of comments, by section, and copies of original comments. Also included is one comment submitted by a public reviewer.

Committee Members/Alternates:	Vote:
Allen Alfrey, M.D. VA Medical Center	Affirmative
Albert Babb, Ph.D. University of Washington	Affirmative
David Berkowitz ECRI	Affirmative
James Boag Colorado Medical	Affirmative with Comments
William Burkinshaw Culligan USA	Affirmative
Sally Burrows-Hudson, R.N. ESRD Network #3	Affirmative
Louis Cosentino, Ph.D./LeRoy Fischbach Renal Systems	Not Voting
Clarence Daly American Society of Hospital Central Service Personnel	Not Voting
Norman Deane, M.D. Manhattan Kidney Center	Affirmative

William H. L. Dornette, M.D., J.D./ Bonnie L. Eckart, CCSM International Association of Hospital Central Service Management, American College of Legal Medicine	Abstain
William J. Dorson, Jr., Ph.D. Arizona State University, American Society for Artificial Internal Organs	Not Voting
Ronald E. Easterling, M.D. American Society for Artificial Internal Organs/Hurley Medical Center	Affirmative with Comments
Martin S. Favero, Ph.D./Lee Bland Centers for Disease Control	Affirmative with Comments
Jerry Fisher Travenol Laboratories	Affirmative
Michael Fisher/David A. Ogden, M.D./ William Litchfield National Kidney Foundation	Affirmative with Comments
Katie Fox, R.N. American Medical Products	Not Voting
Lois Foxen, R.N. St. Joseph Hospital Renal Center	Affirmative
Richard Freeman, M.D. Renal Physicians Association	Not Voting
Robert Galonsky SUNY Downstate Medical Center	Affirmative
Frank Gotch, M.D. Ralph K. Davies Medical Center	Not Voting
Marilyn Case Gould, Ph.D. Associates of Cape Cod, Inc.	Affirmative with Comments
Betty Hanna/Sue Lane Johnson International Association of Hospital Central Service Managers	Affirmative
Gladys Hirshman, M.D. National Institutes of Health	Not Voting
Albert E. Jarvis, Ph.D./James Dugan CD Medical, Inc.	Affirmative with Comments
Prakash Keshaviah, Ph.D. Minneapolis Medical Research Foundation	Not Voting

Lawrence Kobren/Fernando Villarroel, Ph.D. Center for Devices & Radiological Health, FDA	Affirmative with Comments*
Stephen B. Kurtz, M.D./John Mitchell, M.D. Mayo Clinic	Affirmative
Robert Laning, M.D. Veterans Administration	Not Voting
Nathan Levin, M.D. Henry Ford Hospital	Affirmative with Comments
Ben J. Lipps Seratronics	Affirmative
Douglas A. Luehmann Hennepin County Medical Center	Negative
A. Peter Lundin, M.D./Murray Klavens/ Stuart Kaufer National Association of Patients on Hemodialysis and Transplantation	Affirmative with Comments
Curtis Lynch, M.D. The Sporicidin Company	Not Voting
Barry Mason Hemodialysis	Not Voting
Joseph H. Miller, M.D. VA Wadsworth Medical Center	Affirmative with Comments
Edwin A. Pecker Arts and Science Technology	Not Voting
Seymour Perry, M.D. Georgetown University Medical Center	Not Voting
Vincent Pizziconi, Ph.D. Arizona State University	Negative**
Marie Reid Center for Devices & Radiological Health, FD:	Not Voting
Emily Rinehart-Smith Association for Practitioners in Infection Control	Not Voting
Martin Roberts, Ph.D./Frans Van Antwerpen, Ph.D. Organon Teknika	Affirmative
Rosemary Roth, R.N. Association of Operating Room Nurses	Not Voting

Michael Rzeppa Plymouth, MI	Abstain
John Sadler, M.D. University of Maryland Hospital	Affirmative with Comments***
Thomas K. Sawyer, M.D. Northwest Kidney Center	Abstain
Luke Schmieder Mesa Medical	Affirmative
Donald Schoendorfer, Ph.D. HemaScience Labs, Inc.	Affirmative
Robert W. Schrier, M.D. American Society of Nephrology	Abstain
Marshall Smith Sarns	Not Voting
Dean Spatz/Mark A. Paulson Osmonics	Affirmative
Donald Stephens Drake Willock Division, CD Medical, Inc.	Affirmative
James Stewardson/Vera Buffaloe Cobe Laboratories	Affirmative
Marilyn Urps/C.W. Miller National Association of Nephrology Technologists	Negative*
Douglas L. Vlchek Hospal Medical Corporation	Not Voting
David Wagner Computer Dialysis Systems	Not Voting
Elizabeth Whipple, R.N./Dawn Brennan, R.N. American Nephrology Nurses Association	Affirmative

Public Commenter:

Etty Dolin, R.N.
Community Hemodialysis Units

* Alternate submitted comments.

** Comments same as submitted August 1984 - see Attachment 2 to minutes.

*** Minor reservations and clarifictions presented at 30 April 1985 subcommittee meeting.

From: James J. Park, Division of Gastro/Urology and General Use Devices (DGGD), HFZ-420

To: Mr. Gordon Oxborrow, Minneapolis Center for Microbiological Investigation

Subject: Request for Study Formaldehyde and Glutaraldehyde Toxicity in the Blood.

Date: May 21, 1985

STUDY OBJECTIVE

To provide FDA with data which will establish the fate of and adverse effects from formaldehyde and glutaraldehyde and their metabolites in blood.

NEED FOR THE STUDY

Formaldehyde solutions have been used to disinfect dialyzers in the hemodialysis treatment of end-stage renal disease (ESRD). The practice of reusing dialyzers has been limited to a few dialysis centers in the past, but the reuse of dialyzers is rapidly increasing. At the present time, about half of the dialysis procedures performed in the U.S. are done with reused dialyzers. There are over 70,000 ESRD patients treated with hemodialysis in the U.S.. Although the formaldehyde solution is thoroughly rinsed from the dialyzer before the dialysis treatment, trace amount of formaldehyde are always present in the dialyzer and enter patient's blood. The use of glutaraldehyde solution to disinfect dialyzers is limited very few dialysis centers at the present time.

BRIEF SUMMARY REPORT ON FORMALDEHYDE OF HEALTH EFFECTS IN BLOOD

A. CHEMISTRY

Formaldehyde, HCHO, is a colorless, flammable and highly reactive gas with a strong, pungent odor. Formaldehyde is sold mainly as a 37 - 50 % aqueous solution with 1 - 15 % methanol. Reactions with biological materials can involve nucleic acids, proteins, and other amine-containing molecules within the cell.

B. USES AS DISINFECTANT AND EXPOSURE

Formaldehyde is used at low concentration as a disinfectant and preservative. Formaldehyde solution (4 %) have been used to disinfect dialyzers in the hemodialysis treatment of end stage renal disease (ESRD).

C. METABOLISM

Formaldehyde is a normal metabolite in small quantity in mammals. The metabolic pathways for formaldehyde in various animal species are qualitatively the same, but there may be quantitative differences in disposing of exogenous formaldehyde (IRLG, 1981). The major metabolic route appears to be oxidation to formic acid and furthur oxidation to carbon dioxide and water. Additionally, it can enter the one-carbon pool, or act as methyl donor, or can alkylate amines, such as nucleic acids and proteins. Formaldehyde that enters the body appears to be converted rapidly to formate and to combine with tissue(Malorny, 1965;

McMartin, 1979). Formaldehyde also reacts with amines or amides, such as RNA, DNA, and proteins (Heck, 1982; Pruett, 1980). Intravenous (IV) injection of 0.2M formaldehyde into dogs (Malorny, 1965) demonstrated that formate levels in blood rapidly increased during infusion, and formate in plasma reached 14.4 mgr% after 1 h. During infusion, formaldehyde levels were 0.95 mgr% in plasma and 4.06 mgr% in red blood cells. Formaldehyde was not detectable in plasma one hour after infusion. Following infusion of 0.2M formaldehyde into monkeys (McMartin, 1979), the half-life of the formaldehyde in blood was estimated to be 1.5 min. The kinetics of the absorption of formaldehyde by erythrocytes and its conversion to formic acid were studied in rabbits guinea-pigs, rats and mice. Formaldehyde had the biological half-life of 1 min irrespective of species. The half-life of formate varied with species, but was always shortest in the liver (WHO, 1974). Einbrodt (1976) demonstrated a rapid rise of blood and urine formate level in human exposed to formaldehyde. Eels (1981) noted a rise in formate in the blood following ingestion of formalin by a 41-year old woman. Heck (1982) has shown that [14C] formate distributed similarly to [14C] formaldehyde in rat blood cells and plasma following IV injection.

Several studies on metabolic fate of formaldehyde appeared in the literature. Du Vingneaud (1950) found that 80% of subcutaneously administered formaldehyde is converted CO2, while a small amount remained in body tissues incorporated into choline. Neely (1964) administered [14C]formaldehyde intraperitoneally to rats at doses of 7 and 70mgr/Kgr. At a higher dose, 82% of the radiolabel was expired as CO2 after 24 - 48 h and 14% was recovered in the urine. Rats administered IP with 4 mgr/Kgr formaldehyde, 82% was exhaled within 48 h as CO2, while 5.5 % was excreted in the urine. At 40 mgr/Kgr, 78% was exhaled as CO2 after 48 h and 11% was excreted in urine (Mashford, 1982). Five min after oral administration of [14C] formaldehyde to rats, the radioactivity was distributed over the whole body. After 12 hours, approximately 40% had been expired as CO2, 10% had been excreted in the urine and 1% in faeces (WHO, 1974). In WI-38 human fibroblast exposed to [14C] formaldehyde, most of the radiolabel was incorporated into RNA with lesser amounts in DNA and protein (Pruett, 1980). When formaldehyde is inhaled by F344 rats(Heck, 1982), rather tham injected, 40% of the label is retained in the animal, while 40% is exhaled and 20% appears in the urine.

References

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Einbrodt,vonH.J. 1976. Zbl. Arbeitsmed. 26:154-58.
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McMartin,K.E. et al. 1979. Biochem. Pharmarcol. 28:645-49.
Neely,W.B. 1964. Biochem. Pharmarcol. 13:1137-42.
Pruett,J.J. et al. 1980. Arch. Enviorn. Health. 35:15-20.

PLAN OF WORK

The following studies are proposed:

A. Initial Studies

1. Quantitative Analysis of formaldehyde and its metabolites in the blood

Formaldehyde that enters the body appears to be converted rapidly to formate or to combine with tissue. Formaldehyde also reacts with amines or amides, such as RNA, DNA, and proteins. The level of formaldehyde and its metabolites in the blood and plasma should be determined. The metabolism of formadehyde in the blood should be better understood. The distribution, excretion, the storage and effect of formaldehyde in the tissuses should be determined. (If formaldehyde and its metaboltes are not measurable in the blood using established methodology, animals could be used.)

2. Acute Toxicity Studies

Hemolysis has been observed among patients undergoing chronic hemodialysis. The hematologic profile change resulted from the exposure to formaldehyde should be studied (hemolysis, coagulation, erythrocyte and leukocyte distribution and morphology, erythrocyte fragility, thromobocytopenia and effects on other subcomponent of the blood). A complement activation by formaldehyde should be studied. Any allergic reactions should be carefully followed. The gross and micro pathology of formaldehyde exposed tissues should be examined. The "No Observed Effect Level" in human for formaldehyde in the blood should be determined.

3. Chronic Toxicity Studies

Long-term effects of continous low dose exposure to formaldehyde are not known. The chronic toxicity, specially any possible effects on ESRD patients, should be studied in the near future.

4. Assessment of Adverse Health Effects

A. Effects in Animals

B. Effects in Human

DATE 2 JUL 1985
From: Kobren, Lawrence
Dept: OTA-DTD
Tel: 301-443-2436

REUSE. GENE

TO: (@REUSE PMS)
TO: (@OTA REUSE WG)
CC: Arcarese, Joseph S. (JSA)
CC: Morrison, James L. (JXM)
CC: Showalter, Charles (CKS)
CC: Cangelosi, Bob (RJC)
Return-Receipt requested

Subject: Plan of Action -Reuse Policy

RGBO to Jim Chantler
OPSO to Nancy Clements
RANO to Kathy Shanahan
PLNO to Frank Morlock

The issue regarding the need for CDRH to develop a policy on the reuse of medical devices, which we presented at the PMS "Go-Away", has been accepted as a high priority issue by center management. OTA has been designated as lead office and I have been assigned as lead representative for the office. We have not yet made formal requests to the other offices for representatives to work on this issue, so I will assume that the reuse committee members and the OTA reuse working group will continue their active participation unless I am informed by you or your offices to the contrary.

The first order of business will be to outline a plan of operation which will describe how we will develop the policy. For your information, the comments from the senior staff on this issue was, "Policy development necessary. Broad conceptualization should be first step". At this time I'm not exactly sure what they had in mind, but I'll find out and let you know.

I would like each of you to think about this issue and jot down how you think we might proceed. Each office will, I'm sure, have different ideas and priorities and each will have to decide how any policy that is developed would impact on their particular regulatory responsibilities. Also, each will have to decide exactly what should or should not be addressed in the policy.

I plan to have a meeting sometime during the week of July 15th to bring everyone up to date and get your ideas concerning the action plan. I'll get back to you regarding the time and place of the meeting.

P.S.
Don't forget that any plan we develop must include the use of the IHPA conference on the Legal and Public Policy Issues on Reuse to be held this October. We can use this conference to get input from the medical, industrial and legal communities with respect to our proposal to develop a policy and what their concerns about that policy might be.

Have a happy 4th.

Larry

ISSUE STOP PRINT CONTROL SEQUENCE FROM TERMINAL THEN PRESS RETURN

Refer to: FQA-7

JUL 3 1985

Mr. Perry S. Eckel
National Kidney Patients Association
8400 Bustleton Avenue
Suite 3
Philadelphia, Pennsylvania 19152

Dear Mr. Eckel:

This is in reply to your recent letter about coverage and reimbursement for reprocessed (reused) medical mechanical disposable devices.

A recent study conducted by the Association for the Advancement of Medical Instrumentation addresses such issues as hemodialyzer labeling, reprocessing and storage procedures and disposal of rejected dialyzers. The Food and Drug Administration (FDA) is currently examining this study. When we receive the FDA comments, we will consider what steps, if any, should be taken by the Health Care Financing Administration.

Much data has been published which supports the safety and efficacy of reuse. Some of this information was released by the FDA to Mr. Robert Rosen of your organization, in a letter dated August 1, 1984. In case you did not have an opportunity to see it, we are enclosing a copy for your information.

With respect to your comment on the amount the government is paying for reused dialyzers, this issue is fully addressed in the Federal Register of May 11, 1983 on page 21272. We are also enclosing a copy of this document for your information.

Sincerely yours,

Robert E. Wren
Director
Office of Coverage Policy
Bureau of Eligibility, Reimbursement
and Coverage

Enclosures

INTEROFFICE MEMORANDUM

Memo: [46279.3886328.LNK
Date: Fri 2-AUG-1985 10:47
From: Kobren, Lawrence
Dept: OTA-DTD
Tel: 301-443-2436

TO: (@REUSE PMS)
TO: (@OTA REUSE WG)
CC: OTA SENIOR STAFF (@OTA SENIOR STAFF)

Subject: Reuse Minutes

Members Present
Robert Skufca, HFZ-70
Sally Hedrick, HFZ-250
Blix Winston, HFZ-30
Charlotte Silverman, HFZ-104
Evelyn Gordon, HFZ-70
Nancy Lowe-Clements, HFZ-84
Fernando Villarroel, HFZ-420
Norman Wilford, HFZ-420
Bob Handren, HFZ-230

Date: July 18, 1985

Discussions

The Chairman, Larry Kobren, briefed the committee on the "Go Away" presentation and informed us that the development of a more comprehensive reuse policy was considered a high priority issue for the Center during FY-86. Since the reuse policy is a high priority issue, he requested that committee representatives consult with their office directors for their input into OTA's action plan Dr. Villarroel handed out a chart which concisely categorized FDA's possible regulation of reused disposable devices. The committee agreed that General Counsel should be consulted early in the process of developing the reuse policy and a lawyer at least be identified who can work with the committee.

Action Items:

(1) Submit topics for Georgetown Conference to Larry by September 15.
(2) List of terms for the glossary to be submitted to Larry or Sally by August 1 (definition would be appreciated).
(3) Send Larry copies of any articles on reuse that you have in your files. A comprehensive bibliography must be prepared.

Next Meeting: 1:30 p.m., August 8, T-416

ISSUE STOP PRINT CONTROL SEQUENCE FROM TERMINAL THEN PRESS RETURN

Memo: [46296.3338613.LNK
Date: Mon 19-AUG-1985 10:40
From: Kobren, Lawrence
Dept: OTA-DTD
Tel: 301-443-2436

TO: (@REUSE PMS)
TO: (@OTA REUSE WG)
CC: OTA SENIOR STAFF (@OTA SENIOR STAFF)
CC: (@OTA PMS REPRESENTATIVES)

Subject: REUSE MINUTES

********************** Comments: **********************

FYI

************ Forwarded message follows: **************

INTEROFFICE MEMORANDUM

Memo: [46296.2835762.CAD
Date: Mon 19-AUG-1985 07:52
From: Derville, Carole A.
Dept: OSR-OS
Tel: 301-443-4874

TO: Kobren, Lawrence (LNK)

Subject: REUSE MEETING MINUTES

MEMBERS PRESENT:

Blix Winston, HFZ-30
Evelyn Gordon, HFZ-70
Robert Skufca, HFZ-70
Frank Morlock, HFZ-82
Nancy Lowe-Clements, HFZ-84
Charlotte Silverman, HFZ-104
Bob Handren, HFZ-230
Sally Hedrick, HFZ-250
Frank Pipari, HFZ-323
Norman Wilford, HFZ-420
Fernando Villarroel, HFZ-420

RETURN RECEIPT REQUESTED

DATE: August 8, 1985, 1:30 p.m.

Discussions:

The Chairman, Larry Kobren, called the meeting to order and presented OTA's planning schedule for development of the reuse policy. Committee members were asked to confirm their Office's resource commitment for reuse. All did.

Larry also reported that he had been interviewed by Pat Patterson of OR Management and that she would do an article about FDA's reuse policy.

Copies were distributed of a memorandum from Bonnie Malkin on the possible transfer of AIDS by tears and concern that it could be transmitted during the fitting of contact lenses. The Committee suggested that Mr. Villforth might want to include this information in his Georgetown Conference speech.

his Georgetown Conference speech.

On September 4, Mr. Arcarese and Larry will brief Mark Heller, GC, on the reuse policy. Dr. Andersen, OSR, will also be invited to attend the meeting, since OSR will provide legal assistance to the Reuse Committee in developing the reuse policy.

Sally Hedrick distributed copies of the glossary terms that she has compiled with input from Dr. Scufka and Dr. Gordon. Please submit additional terms and definitions to Sally on a continuous basis as she will be updating her list.

There was considerable discussion about whether or not the center had enough data on reuse to develop a reuse policy. It was concluded that the policy could be developed without detailed information on specific device reuse.

Joann Westermeier and Sally Hedrick prepared a listing of all the reuse materials that OTA has in its files. Committee members were requested to send copies of any article/materials on reuse that are not on the list. (Thanks, Joann, for your assistance in setting up a central file on reuse materials.)

ACTION ITEMS:

(1) Send your comments for Mr. Villforth's Georgetown Conference speech to Larry by September 15.

(2) Send glossary terms and definitions to Sally Hedrick as you think of them.

(3) Send copies of any articles not on master list to Sally for reuse central file.

Next Meeting: OPEN

Nancy Lowe-Clements
Secretary

ISSUE STOP PRINT CONTROL SEQUENCE FROM TERMINAL THEN PRESS RETURN

OCT 3 1985

Mr. Robert J. Taylor
Associate Regional Administrator
Division of Health Standard and Quality
Region III
P. O. Box Box 7760
Philadelphia, Pennsylvania 19101

Re: BMA/Capitol Hill
09-2502

Dear Mr. Taylor:

Enclosed is the plan of correction from the BMA/Capitol Hill for the deficiencies cited during the annual certification survey and follow-up visit on March 8, 1985 for the Federal validation survey which was conducted on September 7, 1984.

The delay in transmitting the survey findings to you is due to the difficulties we have encountered in obtaining an acceptable plan from the facility to correct the citations. As you can see, the unacceptable plan of correction is for deficiencies cited in the area of reuse. Since the District does not have any licensure regulations for dialysis facilities or for reuse, and the Federal End-stage Renal Disease regulations do not have clear guidelines on reuse, we are unable to enforce or persuade the facility to follow the standards of practice on reuse established by the Association for the Advancement of Medical Instrumentation or the American Kidney Foundation.

Once again, as we did in our communication with you following the September 1984 Federal validation survey, we request a clear direction from you regarding the position of the Health Care Financing Administration on Reuse. With the exception of deficiencies on reuse, the facility is currently in substantial compliance with all the Federal End-stage Renal Disease Conditions of Participation. Based on the discussion with Mr. James Throne III on September 18, 1985, we are recommending recertification of the facility with the effective date on May 21, 1985.

If you have any questions, please contact Ms. Judith R. McPherson, Program Manager, Health Facility Division, on 727-7190.

Sincerely,

Frances A. Bowie
Administrator

SFRA chron file
Director's chron file
Dictator's copy
Facility file

DCRA/SFRA/YUNG-FATAH/vj/9/27/85

GEORGETOWN UNIVERSITY ANNUAL CONFERENCE ON REUSE OF MEDICAL DEVICES
OCT. 25, 1985

REUSE OF DISPOSABLE MEDICAL DEVICES:
REGULATORY CONSIDERATIONS

by
John C. Villforth
Director, Center for Devices and Radiological Health

I am pleased to be here today and to have the opportunity to talk with you about our concerns related to reuse of disposable medical devices. The Center for Devices and Radiological Health (CDRH) is also pleased that it could assist in the planning of this conference as well as provide some financial assistance.

All of us attending this conference have the same interest; we are concerned that patient safety be maintained through the use of safe and effective medical devices, whether those devices are being used for the first time or are being reprocessed and used on the same patient or on different patients.

Traditionally, FDA's role has been to ensure that the public health is protected from unsafe and ineffective medical devices by regulating the manufacturer. However, reuse is primarily a user practice. FDA, therefore, issued two compliance policy guides to address this practice. One guide, published in 1977 and revised in 1981, discusses the reuse of any disposable medical device labeled "for single use only." It places the responsibility for reuse on the user, by stating that the institution or practitioner who reuses a disposable medical device should be able to demonstrate that: (1) the device can be adequately cleaned and sterilized; (2) the physical characteristics or quality of the device will not be adversely affected; and , (3) the device remains safe and effective for its intended use.

We were confident that this was adequate to protect the public from unsafe or ineffective reused devices because, until recently, hemodialyzers were the only disposable medical device being reused to any significant degree. The reprocessors of these devices were primarily professionals (physicians, nurses, and technicians) who had been reusing hemodialyzers since their inception and had considerable experience reprocessing them. We were also aware of studies which indicated that properly reprocessed hemodialyzers were safe and effective. In addition, FDA was confident that those who engaged in this practice were aware of their responsibilities and that patient safety and device effectiveness of the reused hemodialyzers were being maintained.

The second guide, issued in 1980, was specifically directed at cardiac pacemakers and stated that "the reuse of pacemakers is an objectionable practice", questioning whether pacemakers could be adequately reprocessed.

At present, we are not aware of any reuse of cardiac pacemakers in this country. Apparently, doubt about the legal status of explanted devices in general and pacemakers in particular, a compliance policy that is decidedly negative in tone, and the belief that this country could afford a new pacemaker for every patient probably prevented reuse of these devices.

Recently, however, the pressure to reduce costs by reusing disposable devices has been growing. Our concern is that as more devices are reprocessed by people with less experience in reprocessing techniques, the possibility of adverse effects to the patient increases. For these reasons FDA is developing a more comprehensive reuse policy. We also intend to examine our compliance policy guides to assure their consistency with any new reuse policy.

We at FDA recognize our responsibility in this area. That is why members of my staff have helped in planning for this conference and are participating in it. We believe that the issues concerning the reuse of disposable medical devices are of vital importance and that an open forum such as this is an appropriate medium to discuss these concerns. I would like to emphasize, that those who have a vital interest in this topic will have ample opportunity for comment during the development of any reuse policy.

The Medical Device Amendments of 1976 do not specifically mention the reuse of medical devices. Our task, then, is to determine how the Amendments relate to the reuse of disposable medical devices and to develop a policy based on that interpretation. We will publicize the policy so that the public will be aware of FDA's responsibilities and authority and users (health care professionals, for example), industry, and reprocessors will know what is expected of them. Since FDA's reuse policy is now being defined, we can not make any definitive statements on it at this time. But, I can give you some idea of our thinking and discuss some of the issues that have been raised.

1. Should FDA consider commercial reprocessing facilities to be manufacturers? If so, should hospitals, physicians and clinics which reprocess medical devices be considered manufacturers and thus be subject, at least in principle, to all regulatory requirements. If FDA considers ALL persons or institutions which reprocess disposable medical devices to be manufacturers, would they be required to comply with all the requirements of the Act? Or, should noncommercial reprocessing

facilities be exempted from some requirements, such as inspections and submissions of information prior to marketing (for example 510(k) or PMA's). Should exempted facilities be required to keep records and comply with some or all GMP requirements?

2. Should the requirements for reprocessing of a device that is used for the same patient be different from one used for a different patient? Should the requirements for a device used in the same facility be different from those for one used in another facility? Are the requirements for a device reprocessed in a clinical facility different from one reprocessed in a commercial facility?

3. Another important issue that must be addressed is: Should a manufacturer's claim of "single use" or "disposable" be accepted at face value? Does simply labeling a device for "single use" or "disposable" automatically make it unfit for reuse?

4. What labeling should be required with a reprocessed device? What process controls (GMPs, for example) would be required? Would a reprocessed device be a "new device" or a "new intended use" of an existing device? Or, would reprocessing have no effect on the intended use provisions of the law?

5. Should manufacturers be asked to voluntarily include in their labeling information necessary for those wishing to reprocess and reuse their devices? Such information might include the material properties of the device and the possible effects that temperature and disinfectants might have on the performance characteristics. Should references to acceptable voluntary standards for reprocessing be included in the labeling?

6. Should there be different requirements for reprocessed devices which are exported?

These and many other complex issues have to be discussed within the Agency, and within forums such as this, before any policy can be developed. There are, however, some activities that other organizations can be doing in the interim. Certainly the development of voluntary guidelines for reprocessing disposable devices will go a long way in establishing a benchmark that reprocessors can follow. One example is AAMI's Recommended Practice for the Reuse of Hemodialyzers. Conformance with an accepted voluntary guideline would define the minimum level of reprocessing required to assure safety and effectiveness. This could result in less FDA regulation because those complying with this accepted state-of-the-art would be producing safe and effective devices. With these guides in place, there may be no need for additional regulatory control by FDA.

The Joint Committee on Accreditation of Hospitals could, review a facility's reprocessing procedures to determine compliance with these minimum voluntary standards. In addition, manufacturers could, provide information about their product in the labeling by listing the material properties of the device as well as referencing appropriate voluntary reprocessing standards. We think that information about the material properties a of device is useful, whether or not the device is reprocessed.

The FDA will also be looking into the possibility of educational programs for users, professionals, and patients in the area of reuse in general, and reprocessing in particular. In the area of cleaning and disinfection, generic guidelines could be developed since extensive literature on appropriate methods of cleaning and disinfection of most medical devices exists. However, we think that development of test protocols for specific devices will be necessary to determine the performance criteria that these devices must meet after reprocessing. Finally, we hope to coordinate our activities with the Centers for Disease Control (CDC)and the Health Care Financing Administration (HCFA) to determine if other actions rather than regulation, can be used to monitor and/or control reprocessing.

In summary, let me state clearly that FDA is neither for nor against the practice of reusing disposable medical devices. We are for the safe and effective use of medical devices, whether that device is used as it comes on the market from the original manufacturer, or whether that device is used after being reprocessed. We look forward to continued discussions on these issues and we will be using information from such symposia as this to develop our policy on the reuse of disposable medical devices.

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Infections with *Mycobacterium chelonei* in Patients Receiving Dialysis and Using Processed Hemodialyzers

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and the Hospital Infections Program, Center for
Infectious Diseases, Centers for Disease Control,
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Between April and November 1982, 27 of 140 patients in a hemodialysis center in Louisiana were infected with rapidly growing mycobacteria; 14 had bacteremia alone, 3 had soft-tissue infections, 1 had an access-graft infection, and 9 had widely disseminated disease. Of 26 identified isolates, 25 were *Mycobacterium chelonei* ssp. *abscessus*, and one was an *M. chelonei*-like organism. One factor common to all patients was exposure to processed hemodialyzers (artificial kidneys). Environmental sampling of the water-treatment system showed widespread contamination with nontuberculous mycobacteria, which were also recovered from the patient's side (blood compartment) of five of 31 hemodialyzers that had been processed and were ready for use. The formaldehyde concentration was <2% in two of three such contaminated dialyzers tested. We hypothesize that patients became infected when their blood circulated through processed dialyzers that contained viable rapidly growing mycobacteria. This outbreak demonstrates that hemodialysis patients may be at risk for developing infections with rapidly growing mycobacteria and that such infections may go unrecognized when routine culture methods are used. It also emphasizes the importance of using effective procedures to disinfect dialyzers in hemodialysis centers.

Mycobacterium chelonei and *M. chelonei*-like organism (MCLO) are rapidly growing nontuberculous mycobacteria (NTM) that are widely present in the environment [1, 2]. Recently, their role in human illness has been recognized with increasing frequency [3, 4]. *M. chelonei* has been reported to cause abscesses [5], cutaneous and lymphatic infections [6, 7], pulmonary infections [8], postoperative wound infections [9], prosthetic-valve endocarditis [10], thyroiditis [11], osteomyelitis [12], arthritis [13], and ocular infections [14], while MCLO has been associated with peritonitis in patients undergoing peritoneal dialysis [15].

Infections due to *M. chelonei* and MCLO are usually localized, but disseminated disease has been reported [4, 16–22]. Eight of the 15 reported cases of disseminated infection in immunocompromised hosts have occurred among patients with end-stage renal disease, including four patients undergoing hemodialysis and four renal transplant patients who had undergone hemodialysis up until the time of transplantation. Among the latter group, *M. chelonei* infections were documented two weeks to three months after transplantation.

While patients undergoing hemodialysis are known to be at risk for developing pyrogenic reactions and gram-negative bacteremia if high levels of microbial contamination are present in dialysis fluids [23], infections with rapidly growing mycobacteria generally have not been included among the hazards associated with hemodialysis therapy. Our report describes the clinical, epidemiological, and microbiological characteristics of an outbreak of infections with *M. chelonei* in patients undergoing hemodialysis therapy. The results suggest that infections with rapidly growing mycobacteria may be a potential complication of using processed dialyzers for

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We are indebted to the nurses, microbiologists, and hospital personnel involved in this investigation for their time, assistance, and cooperation.

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hemodialysis therapy. Furthermore, such infections may be difficult to diagnose unless specific cultures for mycobacteria are obtained.

Patients and Methods

All patients undergoing outpatient hemodialysis therapy in one city in Louisiana attended one of two dialysis centers. The centers were managed by the same corporation and staffed by the same nephrologists, but each had a separate team of nurses and renal technicians. Center A, a 26-station unit, opened in 1975; all patients were dialyzed at this center until center B, a 12-station unit, opened in June 1982. At the time of the investigation, 110 patients were being dialyzed at center A and 30 patients at center B. All patients were hemodialyzed ~4 hr per day on one of three shifts, three times a week (either Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday). Most patients were randomly assigned to a dialysis station and nurse on each visit.

Beginning in December 1981 at center A and on opening in June 1982 at center B, all new hemodialyzers (artificial kidneys) were routinely processed before use in center A to prevent "new dialyzer syndrome." The processing procedure was done after each shift and included rinsing the dialyzer with water, rinsing and filling with 2% aqueous formaldehyde, storing for ~48 hr, and then rinsing with sterile saline. Also in December 1981, the centers began a program of dialyzer reuse. Most patients used their dialyzer more than once, with each dialyzer undergoing the same processing procedure described above between uses.

Case definition and selection. In August 1982, after four patients receiving hemodialysis were found to have infection with *M. chelonei*, an investigation was initiated. We defined a case as any hemodialysis patient from whom rapidly growing mycobacteria was isolated. To find cases, we reviewed all clinical microbiology reports for 1982 in the five hospitals in the area and all records of NTM isolates submitted to the Louisiana State laboratory for the years 1979-1982. We also reviewed for unexplained fever all the charts from outpatients receiving hemodialysis in the year 1982; all records of hospital admissions for hemodialysis patients for fever, sepsis, and possible infection, from January 1980 through December 1982; and the results of cultures of blood from outpatients receiving hemodialysis from January 1980 through December 1982. Furthermore, we began active surveillance for rapidly growing mycobacterial infections, including obtaining cultures of blood from 30 asymptomatic patients and from all patients receiving hemodialysis who had a fever >37.8 C or unexplained constitutional symptoms.

Bacteriologic investigation. Before the investigation, methods for culturing blood included using either standard trypticase-soy broth incubated for 14 days and monitored by visual inspection and routine subcultures, or Bactec® media (6B, 7C; Johnston Laboratories, Cockeysville, Md) incubated for seven days and monitored by radiometric measurements on a Bactec semiautomated instrument. Modifications implemented in August 1982 to enhance the recovery of acid-fast organisms included using only radiometric techniques for culture of blood and holding cultures for at least two weeks, with daily readings on days 1 through 7 and on day 14. Culture fluids were routinely stained for acid-fast organisms and subcultured onto Lowenstein-Jensen media on days 3 and 14 and at any time the Bactec reading was positive. Subcultures on Lowenstein-Jensen media were held for an additional 14 days before being reported as negative. Specimens other than blood were tested for mycobacteria by using standard microbiological procedures.

All acid-fast organisms isolated were identified to species, subspecies, and biovariant [24]. Organisms were tested for susceptibility to antimicrobial agents by using a Mueller-Hinton broth-dilution method [25] and for susceptibility to formaldehyde [26].

Case-control study. The case-finding methods described above revealed no evidence that infections with rapidly growing mycobacteria were occurring in patients other than those undergoing hemodialysis. Therefore, we undertook a case-control study to identify risk factors for the development of such infection in patients undergoing hemodialysis. For each patient, three or four controls matched for age, sex, and race were selected randomly from patients undergoing hemodialysis on an outpatient basis who had had no fever in 1982 and who had been receiving treatment in the dialysis center for at least four months before onset of illness in the matching case.

Patients and controls were interviewed and were questioned about their occupation, travel history, and exposure to water at home. Outpatient records were reviewed for underlying renal disease and other medical problems; length of time they had been having hemodialysis; history of kidney transplantation; history of immunosuppressive medications and medications received during dialysis; day and shift of dialysis; location, type, and age of access graft, in addition to where it had been inserted and by whom; dialyzer type, dialysis station, and nurse assigned for each day of dialysis for the one-month period preceeding onset of illness in the respective patient; and blood-urea nitrogen, creatinine, and total white blood cell count during that same one-month period. Data from the case-control study were analyzed statistically in a matched fashion by using a multivariate logistic regression model [27].

Environmental and laboratory investigation. The staff in both centers were interviewed about the design of the water-treatment systems and procedures used to disinfect water-distribution lines and hemodialysis machines, to process and disinfect dialyzers, and to dialyze patients. Also, the records of standard plate counts done to monitor the microbiological quality of the water used to prepare dialysis fluids and to process dialyzers were reviewed.

Water samples from multiple sites throughout both dialysis centers were collected in sterile plastic bottles, refrigerated, and assayed for microbial contamination within 48 hr of collection. Dialyzers that had been processed and were ready for use were tested for microbial contamination and formaldehyde concentration by using a test based on Schiff's reagent [28]. All samples were assayed with either a total-count water tester or a standard membrane-filter technique with filters placed on Middlebrook and Cohn 7H10 agar. After incubation for two to three weeks at 37 C, colonies were counted and acid-fast stains of each colony type were performed. Representative acid-fast organisms were subsequently characterized as described above.

Results

Epidemiological and clinical investigation. Between 16 April and 11 October 1982, infection with rapidly growing mycobacteria was documented in 27 (19%) of 140 hemodialysis patients at the two centers (figure 1). The attack rates were equal for the two centers. Twenty-three cases were identified by the prospective surveillance program implemented in August 1982 and four by the retrospective review of laboratory records and patients' charts. The median age of the infected patients was 58 years (range, 29-81 years); 16 were male and 17 were black. The organisms isolated from the patients were identified as *M. chelonei* ssp. *abscessus* in 25 cases and as an *M. chelonei*-like organism in one case. The acid-fast organism isolated from one patient was not available for identification.

The clinical features of *M. chelonei* infection included fever (88%), malaise (83%), and anorexia (71%). White blood cell counts ranged from 3.0 to 13.9 (median, 6.8) and differential counts were normal. In 12 of 12 cases tested, chest radiographs showed no evidence of active pulmonary disease. Nine of 27 patients had erythema nodosum; biopsies of these skin nodules were culture-positive for *M. chelonei* ssp. *abscessus* in three of three patients tested. Patients with subcutaneous abscesses had single lesions; in one patient the abscess developed at a site of previous soft-tissue trauma. The clinical course and severity of illness varied considerably but correlated with the frequency of isolation of NTM from blood specimens, as well as incubation time needed to detect a positive culture (table 1).

Most antimicrobial agents were inactive against

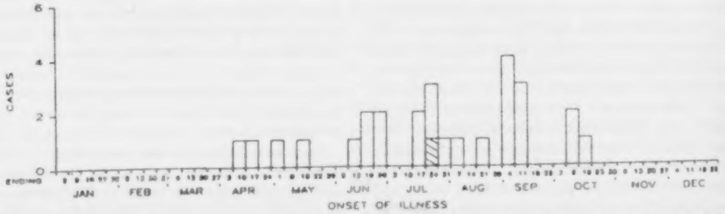

Figure 1. Outbreak of infections with *Mycobacterium chelonei* in hemodialysis patients, Louisiana 1982. Unshaded area represents infections with *M. chelonei* ssp. *abscessus*, hatched area represents infections with *M. chelonei*-like organisms.

Table 1. Isolation of rapidly growing mycobacteria from radiometric blood cultures of patients with various degrees of illness followed for a two-month period.

Mycobacterial illness (*n*)	No. of positive cultures	Total no. of cultures (%)	Median days of culture of blood prior to first positive culture
Disseminated disease* (7)	39	56 (70)	5
Symptomatic bacteremia (4)	9	30 (30)	7
Asymptomatic bacteremia (3)	3	18 (17)	21
Localized abscess (3)	0	20	. . .
Localized graft infection (1)	0	8	. . .

* Infection was documented at multiple sites, including skin nodules, bone marrow, blood, and hemodialysis access grafts.

M. chelonei ssp. *abscessus* in vitro except amikacin and kanamycin; the MCLO was more susceptible to all drugs tested except sulfamethoxazole. Patients thought to have transient bacteremia or localized infection were not given antimicrobial agents. Subcutaneous abscesses were excised and drained, and infected hemodialysis grafts were surgically removed. Patients with symptomatic bacteremia or disseminated disease initially received amikacin and doxycycline or sulfamethoxazole. In general, if symptoms or positive cultures persisted for more than two months, cefoxitin was added to the treatment regimen. Seven patients with bacteremia caused by *M. chelonei* ssp. *abscessus* were followed up for six months while receiving antimicrobial therapy; symptoms persisted and blood cultures remained positive in five patients. In the patient with MCLO bacteremia, symptoms resolved and repeated cultures of blood were negative. In the patient with localized infection of an access graft site, recurrent infection developed at another access-graft six months after the removal of the first infected graft.

Between June 1982 and June 1983, 14 (51%) of 27 patients with multiple underlying medical problems died; seven patients died while receiving antimicrobial therapy for infections with *M. chelonei*, including three who had positive cultures of blood during the two weeks before their death; seven patients died while not receiving antimicrobial agents, including four who died before cultures of their blood were reported to be positive for *M. chelonei*. The only autopsy performed was on a patient receiving no antimicrobial treatment, and no evidence of infection with *M. chelonei* was found.

Case-control study. Data from 23 cases and 58 controls were analyzed in a matched fashion, and four factors were found to be independently associated with the development of infection with *M. chelonei*. Patients with infection were more likely to have been dialyzed on a Monday-Wednesday-Friday schedule (18 of 23 cases vs. 27 of 58 controls, $P = .0238$), although shift of dialysis was not found to be a risk factor. Manipulation or insertion of a hemodialysis graft in 1982 was more common in cases than controls (10 of 23 vs. 6 of 58, $P = .0444$), as was previous hospitalization in 1982, excluding hospitalization for graft manipulation or insertion (12 of 23 vs. 17 of 58, $P = .0014$). Type of access-graft used, surgeon inserting the graft, and hospital in which the graft was inserted did not differ for cases and controls. In addition, a higher proportion of cases than controls (12 of 23 vs. 15 of 58, $P = .0348$) were exposed to nurse 18. A review of employee work schedules and patient-care procedures showed no difference between nurse 18 and the other nurses in number of hours worked on Monday-Wednesday-Friday vs. Tuesday-Thursday-Saturday or in routine patient-care procedures.

No other factors investigated were significantly associated with infection with *M. chelonei*. One factor common to all patients, however, and therefore not examined in the case-control study, was exposure to processed dialyzers. In addition, information regarding the number of times the dialyzer had been reused before the onset of the infection with *M. chelonei* was not available.

Environmental and laboratory investigation. Water used in center A underwent on-site purification. Chloramine-treated municipal water was passed through a sand filter and a reverse osmosis unit and then was stored in two 500-gallon tanks. Upon demand, treated water was pumped from the storage tanks through an activated-carbon filter and a particulate filter to proportioners for diluting dialysate concentrate; the remaining water went from the storage tanks through a particulate filter to the dialysis processing room for rinsing dialyzers and for preparing the 2% formaldehyde solutions. The water-treatment system in center B was identical to that of center A for water used to dilute dialysate concentrate. Negative pressure, single-pass dialysis machines and hollow-fiber dialyzers were used in both centers.

Table 2. Nontuberculous mycobacterial isolates from fluids associated with water-treatment systems and procedures for processing dialyzers.

Environmental source	No. of organisms (cfu/100 ml)	Type of organisms isolated* A	B	C	D	E
Water treatment system room						
Municipal water supply	4.6 × 10^3	–	–	–	+	–
Sand filter	6.1 × 10^3	+	+	–	+	–
RO unit	1.3 × 10^1	–	+	–	+	–
RO storage tank	1.3 × 10^4	–	+	+	–	–
Repressurization tank	7.0 × 10^3	–	+	–	–	–
Carbon filter	2.4 × 10^6	+	+	–	–	+
Proportioner	3.8 × 10^4	+	–	–	–	+
Dialysate	1.7 × 10^6	+	+	–	–	+
Hemodialyzer processing room						
RO line to processing room	1.2 × 10^6	+	+	–	–	–
RO taps for rinsing dialyzers (mean number of cfu from samples collected from 10 taps)	9.0 × 10^4	+	+	+	–	+

NOTE. RO, reverse osmosis.

* Type A = *Mycobacterium cheloneis* ssp. *abscessus*; type B = *M. chelonei*–like organism; type C = *M. scrofulaceum*; type D = *M. gordonae*; type E = mixed population of gram-negative bacteria.

The distribution system for dialysis fluid and dialysis machines were routinely disinfected with a sodium hypochlorite solution for ~30 min every night and with a 1% aqueous formaldehyde solution for at least 24 hr every weekend. Samples of water used to rinse dialyzers and of dialysate fluid obtained weekly and tested for bacterial contamination were consistently reported negative during 1981 and 1982.

Nontuberculous mycobacteria, including both *M. chelonei* ssp. *abscessus* and MCLO, were found in samples of water from multiple sites in both dialysis centers (table 2). Antimicrobial susceptibility of environmental isolates of *M. chelonei* ssp. abscessus and MCLO and of isolates from patients was similar. Ninety percent to 100% of all organisms isolated from samples of water from the line to the processing room and from the taps used to rinse dialyzers were acid-fast organisms. Conversely, >50% of the organisms from samples obtained from the proportioners and from dialysis fluid collected at patient stations were gram-negative bacteria. NTM were also present in the blood compartment (patient's side) of five of 31 dialyzers sampled after the routine processing procedure. The organisms isolated from the dialyzers were identified as *Mycobacterium scrofulaceum* in three dialyzers, *Mycobacterium gordonae* in one dialyzer, and another rapid grower in one dialyzer. *M. chelonei* ssp. *abscessus* and MCLO were not recovered from the 31 dialyzers sampled. The concentration of formaldehyde was <2% in two of three culture-positive dialyzers tested and was 2% in the third. No NTM were isolated from three other dialyzers with concentrations of formaldehyde >2%.

Formaldehyde susceptibility testing of *M. chelonei* isolates demonstrated that isolates of *M. chelonei* ssp. *abscessus* from six patients and three environmental sources did not survive exposure to 2% formaldehyde for 24 hr. Isolates of MCLO from one patient and six environmental sources, however, did survive such exposure, although they did not survive exposure to 4% formaldehyde for 24 hr.

In both centers, reuse of dialyzers was discontinued in the middle of August 1982 and the water-treatment systems were disinfected with 2% formaldehyde. No new cases of infection with *M. chelonei* have been identified in 34 patients who began dialysis after these interventions.

Discussion

This outbreak of infections with *M. chelonei* in patients undergoing hemodialysis provides information on the spectrum of illness and possible sources of infection in these patients. The clinical manifestions of illness reported here confirm findings previously described in sporadic cases [4, 16–20]. Severity of illness ranged from asymptomatic transient bacteremia to widely disseminated disease; no pulmonary involvement was identified, and localized disease was limited to subcutaneous tissues and hemodialysis access grafts. Although 51% of patients died within one year of this outbreak, only one autopsy was performed and, therefore, the extent to which infection with *M. chelonei* contributed to their deaths is unknown.

While the epidemiological investigation did not identify any one risk factor to account for the outbreak, one factor common to all patients was exposure to processed hemodialyzers. Although *M. chelonei* was not recovered from the dialyzers tested, the most likely source of infection in this outbreak was the water used to process dialyzers. Certain features of the design of the water treatment system, such as the presence of storage tanks, may have led to high concentrations of these organisms in the water used to process dialyzers, and disinfection procedures may have resulted in incomplete eradication of *M. chelonei* from dialyzers. Patients may then have become infected when their blood circulated through processed dialyzers containing viable rapidly growing mycobacteria.

It is clear that patients may have had multiple exposures to *M. chelonei* over an extended period of time; the first patient became ill in April and two other patients did not attend the dialysis center until July. The increased risk of developing infection in patients dialyzed on a Monday-Wednesday-Friday schedule suggests that these patients were exposed to a larger concentration of organisms at one or more points in time, perhaps because of increases in the concentration of these organisms in the water on Sundays (when the system was inactive) or to variations in the concentration of the stock formaldehyde solution used to disinfect the dialyzers or both.

There are reasons for concern that infections with *M. chelonei* may be more commonplace among hemodialysis patients. First, 50% of the previously described disseminated infections with *M. chelonei* have been in patients undergoing or recently having undergone hemodialysis. Second, these organisms, which can survive in potable water and can be relatively resistant to chemical germicides [26], may be present in water used in other hemodialysis centers. Third, these organisms may not be detected by routine culture methods, and infections with *M. chelonei* may go unrecognized. Thirty percent of the cultures positive for rapidly growing mycobacteria reported here showed no microbial growth during the first seven days of incubation and two cultures were without evidence of growth during the first 14 days of incubation; mycobacterial growth was demonstrated only by blind subculturing onto Lowenstein-Jensen media on the fifth and 14th day. Furthermore, mycobacteria from blood cultures may be misidentified on gram stain as corynebacteria or gram-positive cocci and dismissed as a contaminant.

Because the majority of infections in this outbreak were due to *M. chelonei* ssp. *abscessus*, which was susceptible to 2% formaldehyde in vitro, and because concentrations of<2% formaldehyde were found in some hemodialyzers, it is likely that failure to attain this concentration of formaldehyde in the hemodialyzers played a major role in this outbreak. Whether the low levels of formaldehyde measured in the dialyzers were due to a decrease in concentration with time is unknown. Because MCLO resistant to 2% formaldehyde was also isolated as a pathogen in this outbreak, it is possible that exposure to 2% aqueous formaldehyde for 24 hr, as used in many dialysis centers, may not be adequate to disinfect dialyzers before use. In 1982, 43% of 1,017 centers for outpatient hemodialysis surveyed in the United States processed dialyzers for reuse; the majority of centers used 2% aqueous formaldehyde solutions to disinfect dialyzers [29].

In conclusion, any patient receiving hemodialysis who has unexplained persistent fever or vague constitutional symptoms should have multiple blood specimens obtained for NTM cultures by using techniques that enhance the recovery of mycobacteria. Further studies are needed to evaluate factors that affect the eradication of rapidly growing mycobacteria in dialyzers, such as concentration of organisms and concentration and contact time of disinfectants, and to develop appropriate control measures for rapidly growing mycobacteria in hemodialysis facilities. In the absence of mycobacterial infections in patients at a given center, it does not seem reasonable to routinely monitor water-treatment systems for acid-fast organisms. These organisms are widely present in the environment, including potable water, and until further information is available, the significance of isolating rapidly growing mycobacteria from water samples in a hemodialysis facility where there is no evidence of disease is not known.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

P.O. Box 7760, 3535 Market Street
Philadelphia, PA 19101

Refer to: HSQ-R3 (16)

NOV 18 1985

Frances A. Bowie, Acting Administrator
Service Facility Regulation Administration
Department of Consumer and Regulatory Affairs
614 "H" Street, N.W.
Tenth Floor
Washington, D.C. 20001

Dear Ms. Bowie:

In response to your inquiry of October 3, 1985 regarding the official Health Care Financing Administration's (HCFA) position on the reuse of dialyzers and bloodlines in End Stage Renal Disease (ESRD) centers, we offer you the following:

> There is no official policy with respect to reuse in ESRD facilities participating in the Medicare program at this time. The survey report form HCFA 3427 addresses the issue at data tag V186 and stipulates that each facility reusing dialyzers must have a written policy stating the number of times or the anticipated efficiency level permitted for reuse as well as procedures for appropriate and effective sterilizing and storing. Other than the guidelines and the provisions of the survey form, we can offer you no other written criteria on the subject as it pertains specifically to the certification process.

Our central office is aware of the issues and of your concerns (see attached Memorandum of 7/3/84). In our most recent contact with them, we learned that the draft results of a study by the Association for the Advancement of Medical Instrumentation (AAMI) regarding reuse practices has been published and is now in circulation for public comment. Representatives from Health and Human Services are submitting comments on the study findings. We have also been informed that HCFA regulations, policy issuances, etc. will not be amended or changed until all results are finalized. It is anticipated that ESRD program modifications will be forthcoming sometime in 1986 based on the AAMI effort.

We will keep you informed of any action in this regard.

Should you have any questions, please contact Sally Robins at (215) 596-6957.

Sincerely,

Claudette V. Campbell

Claudette V. Campbell, Chief
Survey and Certification
Review Branch

NATIONAL KIDNEY PATIENTS ASSN.
WE HAVE MOVED
OUR NEW ADDRESS IS
SUITE 102
#2 PARK LANE
FEASTERVILLE, PA 19047

November 19, 1985

Governor Thornburgh
Office of the Governor
Harrisburg, PA

re: Re-use of Medical Disposables

Dear Governor Thornburgh:

We have been fighting for Kidney Patients for over three years.

During that time, we had written to you on numerous occasions. We had written and met with the Department of Health; written and met with your Renal Advisory Committee; written each and every member of the Legislature and met with perhaps one half of them. We are at our wits end, and find that in spite of our efforts, we are now caught up in a political game. As more and more money pours into the hands of lobbyists, our chances to help patients fade into infinity.

I am weary of the government shuffle. Each person we speak to reacts in exactly the same manner. They are appalled by what is happening and outwardly pledge their support. Unfortunately, they never take any action to help rectify the situation.

The entire issue of re-use has gone totally out of control. In an attempt to further the financial goals of the large corporations and/or the physicians, a vast network of medical abuse has erupted. This unspeakable horror is known by all. Is it any different or less acceptable than child abuse? These poor patients are being threatened with the very loss of life and limb.

It is time that you get involved. It is time for the Department of Health to cease shirking its responsibility to the public Lives are hanging in the balance while everyone in Harrisburg prays that another department will try to correct it. The buck stops at the top and your office is representative of the most powerful in the state. You have the means to save lives and reinvest the patients with the dignity that has been taken away.

Quality Medical Care... Nothing Less!

NATIONAL KIDNEY PATIENTS ASSN.
WE HAVE MOVED
OUR NEW ADDRESS IS
SUITE 102
#2 PARK LANE
FEASTERVILLE, PA 19047

The purpose of this letter is to obtain an audience with you personally to discuss this situation at length. Please understand that I am writing this letter at the insistance of my Board of Directors. The patients have given me a deadline of December 5, 1985 to arrange our meeting. If I report my inability to arrange this conference, they have vowed to mobilize and come to Harrisburg in mass. They are angry and cannot tolerate the treatment they are receiving at the units.

As you may or may not know, a dialysis patient must receive a treatment three times a week. In the event that treatment is not rendered, the patient will die. They have vowed to sit in the hall outside of your office and remain there until they die in front of 60 million TV viewers. No one wants to see this type of thing happen.

I am positive that this rather rash action is totally unnecessary. It merely proves the necessity of personally meeting to attempt to resolve issues.

Please respond to my request at your earliest convenience.

Thank you for your courtesy and cooperation.

Very truly yours,

Perry S. Ecksel

PSE:dl

CC: Gail Evans, CNN
Mimi Evans, 60 Minutes
Don Wolf, Caukins News Service
Bonnie Rabden, Philadelphia Daily News
Linda Herskowitz, Philadelphia Inquirer
Norris West, Philadelphia Tribune
Rick Williams, Channel 6 - TV
Janet (Lulu) Laubenstein, Channel 3 - TV
Assignment Desk, Channel 10 - TV
Board of Directors, National Kidney Patients Association

DEPARTMENT OF HEALTH & HUMAN SERVICES
Health Care Financing Administratio

6325 Security Boulevard
Baltimore, MD 21207

DEC 4 1985

FQA-422

Mr. Perry S. Ecksel
National Kidney Patients Association
Suite 102
No. 2 Park Lane
Feasterville, Pennsylvania 19047

Dear Mr. Ecksel:

This is in response to your letters to the Secretary regarding reuse of hemodialyzers. Please forgive the delay in my reply.

I appreciate your interest in this issue, which is of concern to many Medicare end-stage renal disease beneficiaries and to the Health Care Financing Administration (HCFA) as the primary payor for dialysis services.

While the general question of reuse is a medical practice issue and one which should be decided by the patient's physician, much data has been published which supports the safety and efficacy of reuse. A recent study conducted by the Association for the Advancement of Medical Instrumentation addresses such issues as reprocessing material, hemodialyzer labeling, reprocessing and storage procedures and disposal of rejected dialyzers. The FDA is currently examining this study. When we receive the FDA comments, we will consider what steps, if any, should be taken by HCFA.

As you may know, the State surveyors of Medicare facilities that reuse hemodialyzers do check to determine whether facilities have a written policy covering the number of times dialyzers can be safely reused, including procedures for the cleaning, sterilizing and storage of dialyzers. You may wish to contact the Pennsylvania Department of Health, 1937 New Hope Street, Morristown, Pennsylvania 19401, about your concerns.

I am bringing this matter to the attention of our regional officials in Philadelphia for their consideration.

Sincerely yours,

Robert A. Streimer

Robert A. Streimer
Acting Director
Bureau of Eligibility,
Reimbursement and Coverage

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

Dec. 4, 1985

Association for the Advancement of Medical Instrumentation
1901 N. Fort Meyer Drive
Suite 602
Arlington, Virginia 22209

Dear Sir/Madam:

The Center for Devices and Radiological Health (CDRH), Food and Drug Administration, has recently reviewed its staff participation on non-Government committees. We would like to nominate the individuals listed in the enclosure as CDRH representatives for participation in your organization's standards development activities.

All nominees may be considered as voting representatives and their written ballots will reflect the views of the Center for Devices and Radiological Health. The policy of the Food and Drug Administration, however, stipulates that participation by these representatives shall not necessarily reflect the agreement of the Food and Drug Administration with, nor endorsement of, any decision reached by the committee.

We appreciate the opportunity for continued participation in the activities of your organization. If you have any questions or if there are any errors in our Committee nomenclature, please contact Mr. James J. McCue, Jr., Center for Devices and Radiological Health, 5600 Fishers Lane, Rockville, Maryland 20857 (301) 443-4874.

Sincerely yours,

John C. Villforth
Director
Center for Devices
and Radiological Health

Enclosure

WORKING PAPER: POLICY CONSIDERATIONS FOR THE REPROCESSING OF DEVICES

[Food And Drug Administration]

Reuse Committee

2/24/86

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PURPOSE

The apparent widespread reuse of certain medical devices has led to questions concerning the position of FDA with respect to this practice. Accordingly, the Reuse Committee has developed this working paper to clarify the applicable legal requirements and to specify actions that may be taken by FDA with respect to reuse of devices. Although Public Law 94-295, the Medical Devices Amendments of 1976, makes no mention of the Agency's specific authority with respect to reuse of medical devices, the committee believes that FDA has the authority under the existing law to regulate processing of devices for reuse whether it is carried out by the original manufacturers, health professionals or others.

The reuse of medical devices is a practice which have raised legal, ethical, economic, technical and safety questions. The practice of reuse has become more widespread in recent years because of the increasing pressure to contain costs in the health care field. While the committee recognizes the economic aspects of reuse, the proposed reuse policy described in this paper does not address the cost issues.

The Reuse Committee believes that the decision to reuse a medical device is a medical decision which FDA should not interfere with. However, once that decision is made the reprocessor, whether that reprocessor is the original manufacturer or a user of a medical device such as a physician or clinical facility, must assume the responsibility for assuring that the device is safe and effective after processing for reuse. The Reuse Committee also believes that FDA has a responsibility under the Medical Device Amendments, and the broader aspects of the Public Health Service Act, to assure that the public is protected from unsafe and/or ineffective medical devices whether those devices are new or reprocessed. The reuse committee believes that the manufacturer of the original unused device also has an obligation to provide certain information with respect to that device to the purchaser.

The goal of this policy is to assure that the reliability of a device that has been processed for reuse is not compromised by the process. We believe that in order to reach this level of reliability requires mutual interaction between the manufacturer and the persons who choose to reprocess that device. This paper therefore discusses a proposed policy which the Reuse Committee believes defines FDA's statutory authority and limitations with respect to the reuse of medical devices, the responsibilities of the reprocessor and the original manufacturers, and the actions that could be taken to assure the safety and effectiveness of medical devicesprocessed for reuse.

DEFINITIONS

Reuse: The process whereby a medical device, regardless of its labeling, is used more than once on the same patient or on different patients.

Used Device: A device which has been used in the manner intended by the original manufacturer.

Process for Reuse (Reprocess): To subject a device to a special protocol in preparation for reuse. This normally includes cleaning, disinfection or sterilization, and testing of the device.

Reprocessor: The person or facility that processes a device for reuse.

Device Categories with respect to Reprocessing Potential:

Type I: Non Reprocessable Devices

Devices considered not to be capable of being processed for reuse because their design and/or materials precludes the device from being adequately cleaned, disinfected and/or sterilized; or whose materials deteriorate to such an extent after the first use that adequate reprocessing is not possible.

Type II: Potentially Reprocessable Devices

a) Devices that have traditionally been reprocessed or have been shown (through experience or scientific evaluation) to be capable of safe and effective reuse if proper reprocessing is performed.

b) Devices considered capable of being reprocessed but for which there are no established reprocessing protocols. The reprocessor needs to establish for these devices effective reprocessing and test procedures to assure that the reprocessed device is safe and effective for its intended use.

c) Devices whose sterility may have been compromised, but which have not been used by a patient.

Disposable: Suitable for eventual discard. The use of this term in the labeling of a device does not limit the number of uses of the device before discarding it. It infers a relatively short life, but is not equivalent to single use.

Single Use: Not suitable for reuse. One use only.

Original Manufacturer: The manufacturer of an unused device.

BACKGROUND

The reprocessing of medical devices that have been previously used by a patient is not a new practice. Prior to World War II, most medical devices were manufactured with the intent that they would be reused. Devices were made from durable materials that could be cleaned and then sterilized in steam autoclaves or properly disinfected. In fact, this practice presumed that the hospital or physicians in their offices would clean, disinfect or sterilize, and test as necessary the performance characteristics of the device before returning it to service. Even then, some products were not reused either because they were destroyed during their first use or because tests revealed that certain characteristics of the device had diminished, as a result of use or reprocessing, to a point which prevented their acceptability.

Since reprocessing devices was labor intensive and time consuming for the user, the industry begun to provide the health care facilities with presterilized items such as syringes, rubber gloves, tubing, masks, etc. which were labeled "disposable" or "single use" (these terms were considered equivalent). These items were presumed to be discarded after a single use because it was more efficient and economical to do so. Later, the manufacturers of medical devices began to replace the more durable materials used in medical devices such as glass and metal with plastic. Devices made from plastic materials were cheaper and easier to fabricate and were sold at prices which allowed them to be discarded after use. Many of these early plastic materials could not withstand steam sterilization without altering their mechanical properties, thus, the industry switched to ethylene oxide (ETO) as the primary means of sterilization. As a result of these changes, and since many hospitals did not have ETO sterilizers, these medical devices were automatically discarded after use, primarily due to the lack of resterilization facilities. Nevertheless, the fact that these devices were cheap enough to discard did not necessarily mean that they could not be reprocessed if adequate facilities existed at the hospitals.

Today, many health care facilities have ETO sterilizers and have also developed skills in the use of highly effective liquid chemical disinfectants. These facilities are capable of reprocessing a variety of medical devices some of which may include in the labeling the terms "single use" or "disposable". Administrators, physicians and others who must now reduce the operational costs of their facility, have focused on the reuse of "disposable" devices and have suggested that many items, which the hospitals had originally reprocessed but which may have become "single use" or "disposable" by default, could be reprocessed as a cost-saving measure. Whether or not economies result, depends on many factors including the original cost of the item, and the cost of reprocessing. The Reuse Committee believes that the most important factor that the reprocessor must consider, however, is whether the device can be processed for reuse in a manner which will enable it to be used safely and effectively in the manner intended by the original manufacturer. It makes no difference to the patient if a device comes from a factory, from the hospital's central supply service, or whether it is labeled "single use" or "disposable". What is important is that the patient is assured of the safety and effectiveness of the device regardless of who provides it or how it is labeled.

INTENDED USE

The Reuse Committee recognizes that many manufacturers include "single use" (or words to that effect) within the meaning of "intended use". The manufacturers suggest that their intent in designing a device is to produce a device that will perform a specific function, and will be used only once and then discarded.

The Reuse Committee believes, however, that the meaning of "intended use" as stated in 21CFR 801.4 does not allow for such an interpretation. 21CFR 801.4 discusses "intended use" and refers to the "objective intent of persons legally responsible for the labeling of the device". The Committee believes that this refers to the primary reason that the device was designed. Under the law, the manufacture and subsequent marketing of the device must be supported by valid scientific and engineering data and experience which provides reasonable assurance that the device will safely and effectively perform the function for which it was designed. The "intended use" for a pacemaker, for example, is to provide pacing for a defective heart. The scientific issue of whether or not any medical device can be reused depends on the ability of the device to perform in a manner that is acceptable after reprocessing. The Reuse Committee believes that the characteristics of the device, not an arbitrary statement in the labeling, should determine whether or not a device can be reprocessed without impairing its performance. An arbitrary, unsupported statement in the labeling claiming that the device is for "single use" should not be regarded as indicating that the device cannot be reprocessed. Thus, the Reuse Committee believes that the statement "single use" does not reasonably belong under the definition of intended use provided in 21 CFR 801.4, but rather under "adequate directions for use" (21 CFR 801.5 and 801.109(c)).

Also, the Reuse Committee believes that the terms "disposable" or "sterile" are not equivalent to "single use" and should not be included in the labeling to indicate that the device ought to be discarded after one use (see definitions).

MANUFACTURER'S RESPONSIBILITY

The Reuse Committee recommends, therefore, that directions for use such as "single use" (or equivalent) be reserved for devices which cannot be reused and for which the manufacturer can reasonably support the statement. If the original manufacturer chooses not to provide information on how to process a device for reuse, then the labeling should include a statement indicating that the manufacturer does not recommend the reuse of the device, and state the reasons why. Warnings concerning processing for reuse that the manufacturer may be aware of should also be included in the labeling. The Reuse Committee, also recommends that manufacturers who label their devices as "single use" (or words to that effect), in future premarket notifications or Premarket Approval applications be asked to provide data to FDA to substantiate the statement. This may include data which will show that the design of the device is such that cleaning and/or disinfecting can not be adequately performed, that the materials can not withstand certain temperatures, that exposure to additional disinfectants or sterilants cannot be used without a marked decrease in its performance characteristics, or that the materials that have been selected can be used only for a designated period of time. In any case, the burden for proving that any device labeled "single use" must be disposed of after its initial use, should be on the original manufacturer.

The Reuse Committee is aware that manufacturers may not have investigated the effects that reprocessing would have on the material properties of the device, and therefore should not be required to provide reprocessing information to the purchaser. The Reuse Committee believes, however, that the manufacturer must be aware, or should be, of the performance and material characteristics of their device and how they may have been affected by the manufacturing process they use. In addition, devices which contain materials which, as part of their intended use, contact blood or tissue could be potentially hazardous to the patient due to the patient's reaction to them. In order to minimize these reactions, the patient or his/her physician needs to know what materials are being used or what chemical sterilants or disinfectants the device had been exposed prior to the use by the patient. We believe this is vital patient and professional information and is necessary for the effective use of the device whether or not the device would be reprocessed. The Reuse Committee believes that the manufacturer of any device should provide as a minimum the known information about the materials in the device so that the user would have the data necessary to prevent or mitigate allergic reactions or to develop effective reprocessing protocols if they so desire. Therefore, the Reuse Committee believes that the following information should be included in the labeling of devices not authenticated as "single use":

a) Sterilization process originally used on the device (if sold as sterile);

b) The composition or the chemical names of the materials which make up the device;

c) Possible effects of processing parameters on the materials of the device known, by the manufacturer. For example, precautions concerning effects caused by parameters such as temperature, pressure, and effects of various chemicals (specifically disinfectants and sterilants) may be included.

REPROCESSOR'S RESPONSIBILITY

Federal regulation 21 CFR 820.3(k) defines a manufacturer as "any person, including any repacker and/or relabeler, who manufacturers, fabricates, assembles or processes a finished device"(emphasis added). Accordingly, the Reuse Committee believes that any person who reprocess a medical device, should be considered a manufacturer.

The Reuse Committee believes that for a reprocessed used device to be considered safe and effective, the reprocessor must demonstrate that:

1) The device to be reprocessed has not been demonstrated to be a "single use" device by the original manufacturer;

2) The characteristics of the reprocessed device is not altered by the reprocessing to such an extent that the device cannot be used by a patient in the manner intended by the original manufacturer;

3) The device after reprocessing is safe and effective for its intended use.

Specifically, the use of proper post-reprocessing testing can ascertain whether the characteristics of the device have diminished, as a result of reprocessing, to a point which renders the device unacceptable for the use for which it was originally intended. The Reuse Committee also believes that the reprocessor should be able to show that the reprocessing protocols for cleaning, disinfecting or sterilizing, and testing will ensure that the device can be returned to a state safe and effective for its intended use.

REPROCESSING BY HEALTH CARE FACILITIES

The Act exempts from registration (510(g)), records and reports (519(a)) and the inspection of records for restricted devices (704(a)), practitioners licensed by law to prescribe or use devices, and who manufacture or process devices, solely for use in the course of their professional practice.

However, the Reuse Committee believes that large scale routine processing of devices for reuse performed at health care facilities do not fall within this exempted category. Specifically, the following manufacturing activities should not be considered exemptions within the meaning of 510(g), 519(a) and 704(a):

a) Reprocessing of hemodialyzers in dialysis centers with more than 10 patients treated with reused dialyzers.

b) Reprocessing of devices performed at a central location in a health care facility.

REPROCESSING BY LICENSED PRACTITIONERS

The Reuse Committee believes that practitioners licensed by law to prescribe or use devices, and who manufacture or process devices solely for use in the course of their professional practice should not be considered manufacturers.

The Reuse Committee recognizes that there is a distinction between reprocessing by licensed practitioners and reprocessing by a health care facility, discussed in the previous section. The concept of reprocessing devices by licensed practitioners generally includes devices processed in a physician and dentist private practice, such as sterilization of small instruments, or the processing of custom devices (21 CFR 812.3(b)). The exemptions granted by law and regulations to licensed practitioners should not be extended to the larger reprocessing operation conducted in health care facilities.

REPROCESSING OF CLASS I AND CLASS II DEVICES

Class I and class II devices include preamendment devices, devices which have been marketed through the premarket notification (510(k)) process, and devices which have been reclassified from class III to class I or II. The discussion in this section also includes some preamendment class III devices for which no premarket approval applications (PMA) have been required by the FDA.

The Reuse Committee recognizes that reprocessing raises questions about the safety and effectiveness of the resulting device. However, we believe that for many of these devices which have been in commercial distribution for a number of years, there is a substantial body of information available in the scientific literature to enable a reprocessor to use appropriate methods for cleaning, disinfecting, sterilizing and testing to justify the conclusion that a properly reprocessed device will still adequately perform the function for which it was originally intended and thus, a device processed for reuse should not be considered different in terms of its performance, safety, and effectiveness from the original (unused) device.

The Reuse Committee believes, however, that all reprocessors should be required to comply with Good Manufacturing Practice (GMP) regulations (21 CFR 820) to assure that the reprocessed device continue to be safe and effective for its intended use. The Reuse Committee also recommends that FDA exempt from certain regulatory requirements a reprocessor who reprocesses a device using a protocol (1) recommended by the original manufacturer in the labeling of the device or, (2) which is an accepted practice endorsed by a reputable professional society, and (3) provided that the reprocessing protocols have been validated for the specific device. These exemptions, under Section 510(g)(4) of the Act, should be limited to the following: (a) registration and listing; and (b) premarket notification. Basically, the reprocessing of a device according to (1) or (2) and (3) above, should be considered as a process which does not result in a change or modification of the device that could significantly affect the safety or effectiveness of the device (21 CFR 807.81(a)(3)(i)). These exemptions, however, should only apply to those facilities that reprocess devices for use in their own facility and do not distributed them to other institutions.

Evidence of substantial or unreasonable risks of injury due to improper reprocessing in these facilities brought to the attention of the FDA should be investigated. Inspection (Section 704 of the Act) should be conducted to determine if the device is adulterated, under Section 501, and/or misbranded under Section 502, due to improper reprocessing or from an attempt to reprocess a device whose design is such that it precludes reprocessing. Appropriate regulatory measures such as notification, under Section 518; injunction, under Section 302; or seizure, under Section 304, should be taken to correct the situation.

The use of reprocessing guidelines developed by voluntary standard organizations like the Association for the Advancement of Medical Instrumentation (AAMI) and the American Society for Testing and Materials (ASTM) and others, would be helpful in providing these facilities with appropriate information on the latest state-of-the-art methods for cleaning, disinfecting, sterilizing and testing.

REPROCESSING OF CLASS III DEVICES

The discussion in this section includes all class III devices which have been marketed through a premarket approval application (PMA). It excludes preamendment class III devices marketed through a premarket notification (see previous section).

The Reuse Committee recognizes that devices which were originally marketed through PMA process are regulated under more stringent requirements than the preamendment devices discussed in the previous section. The Reuse Committee proposes that devices for which the original manufacturer included reprocessing instructions in the labeling, may be reprocessed with no other regulatory controls than those imposed on class I and II devices.

Also, devices for which the original manufacturer chooses not to provide reuse instructions may be processed provided that the reprocessing facility obtains an approved PMA from the FDA for the reprocessing procedure.

PROPOSED POLICY

The Reuse Committee proposes the following policy statements:

1. The statement "single use" (or equivalent in the labeling of a device should be construed as within the definition of "adequate directions for use" provided under 21 CFR 801.5 or 801.109(c). This statement should not be construed as within the definition of "intended use" provided in 21 CFR 801.4.

2. The terms "disposable" or "sterile" are not equivalent to "single use", as these terms in the labeling of a device do not necessarily limit the number of uses for a device before discard. These terms should not be allowed in the labeling of devices without an equally prominent, clear explanation of their meaning.

3. The term "single use" (or equivalent) should be reserved for the labeling of devices for which the original manufacturer had provided to the FDA (in a premarket notification or PMA) data proving that the device cannot be reused.

4. The manufacturer of devices which have not been authenticated as "single use" should provide the user with information concerning the material properties of the device, or state that reuse is not

recommend and state the reasons why. As a minimum, the labeling of devices which have not been authenticated by the manufacturer as "single use" should include (a) the sterilization procedure originally used on the device, and the chemical sterilants (if any) to which it may have been exposed, and (b) the composition or the chemical name of the materials which make up the device. Precautions concerning effects caused by parameters such as temperature, pressure, and effect of various chemicals (specifically disinfectants and sterilants) should be included.

5. All persons who process a medical device for reuse should be considered a manufacturer, according to 21 CFR 820.3(k). Facilities which process medical devices for reuse located within health care facilities are considered manufacturers if they perform large scale, routine reprocessing of devices. In particular, routine reprocessing of hemodialyzers should be construed within the activity performed by a manufacturer. Processing of devices for reuse by licensed practitioners, such as disinfection or sterilization of instruments performed by a physician or dentist in private practice, or the reprocessing of devices generally considered custom devices are not considered a manufacturer's activity.

6. A reprocessor of a medical device must demonstrate that (1) the device to be processed for reuse has not been demonstrated to be a "single use" device by the original manufacturer, (2) the characteristics of the reprocessed device is not altered by the processing to such an extend that the device cannot be used by a patient in the manner intended by the original manufacturer, and (3) the device after being processing for reuse is safe and effective for its intended use.

7. Reprocessors of class I, class II, and class III devices which have not been originally marketed through a PMA process (a preamendment device), and are reprocessed by a facility for use exclusively in that facility must comply with GMP regulations according to 21 CFR 820, but are exempted from registration and listing, and premarket notification according to Section 510(g)(4) of the Act. The protocol used in processing these devices must be (1) recommended in the labeling of the original device or, (2) an accepted practice endorsed by a reputable professional society, and (3) validated by the reprocessor with the specific device.

8. Reprocessors of class III devices which have been marketed through a PMA process and whose labeling include instructions for processing for reuse, may process such devices under the same regulatory controls imposed on class I and II devices. However, the reprocessor of a

class III device for which the original manufacturer chooses not to provide instructions for reuse, must obtain an approved PMA from FDA for the reprocessing procedure.

9. Reprocessing facilities that have been established solely for the purpose of reprocessing and commercial distribution of previously used medical devices and that intend to distribute the reprocessed device to clinical facilities or professional practitioners other than those who originally supplied the used device are considered to be manufacturers and are not exempt from any requirements of the regulations.

10. Commercial facilities that reprocess previously used medical devices, and return them to the same facility from which they were received, and which are intended to be used on the same patient or on different patients in that facility should be considered to be manufacturers, and should not be exempt from any provisions of the regulations. In addition, if the commercial facility processes a device and returns it to the same facility from which it was received for use on the same patient, the reprocessor should develop protocols which will assure that the device can retain its identity so that it can be returned to the original patient. Labeling on the device should indicate that it has been processed for reuse, and should also include the name of the facility, the patient's name (or identity code), the level of disinfection and/or sterility achieved, and instructions for preparing the device for use by the patient.

11. Medical devices processed for reuse which are intended to be exported either for charitable purposes or for sale, and which are processed either in a clinical facility or in a commercial facility, should comply with the requirements of Section 801(d) of the Act. In addition, to assure that the exported device is "not contrary to public health", we suggest that the reprocessor comply with the following requirements:

(a) Register with FDA.

(b) The device be inscribed with information indicating that the device has been used and reprocessed and that it is not for import into the United States. If the device cannot be so inscribed, that information must be included in a prominent position on the package.

(c) The exporter should also identify in the registration exactly which device is to be exported and must keep records which will assure that the device can be traced if it is subject to a recall or notification.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date JUL 8 1986

From Director, National Center for Health Services Research and Health Care Technology Assessment

Subject Hemodialyzer Reuse

To Assistant Secretary for Health

ISSUE

As HCFA continues to ratchet down the reimbursement rate for hemodialysis, concern has grown on the part of hemodialysis patients and the Congress, with respect to the safety and efficacy of the reuse of dialysis equipment, including bloodlines, tubing, transducer caps, and filters. Senator Heinz was sharply critical of the Public Health Service's role in this process during hearings which he conducted on March 6 of this year. The involvement of NCHSR is only recent, but NIH, FDA and CDC have had a long but non-productive involvement with these issues. During the March 6 hearing, at which I was the witness for the PHS, accompanied by John Villforth of FDA, we agreed to do an assessment of the state-of-the-art. As events have unfolded, it is clear that the March 6 testimony was not based on all of the germane facts and that we may need to take a position counter to that which we argued on March 6. We need to ascertain a PHS position and inform HCFA of that position so as to minimize embarrassment for the Department.

BACKGROUND

The March 6 hearing focused on the following issues:

1. Does adequate information exist to determine what standards are necessary for adequate disinfection of dialysis equipment?

2. How many uses of a given unit should be permitted before its integrity is compromised?

3. What is the Department doing to monitor adverse effects?

4. Are patients being fully informed of the risks attendant to dialyzer reuse and is their freedom of choice being compromised?

In 1978, the Congress directed NIH to carry out a study of hemodialysis. A contract was let which led to release of the Dean Report in 1981. The Dean Report was subsequently revised in 1982. The essential conclusion of the Dean Report was that processing, when properly effected, could yield a hollow tube filter equivalent to a new filter. Arthur D. Little, Inc. was a subcontractor to this effort and it released a criticism of the Dean report arguing that its efforts had been improperly represented and that the report was limited to an in vitro assessment which ignored clinical data.

In 1982, a departmental Interagency Task Force recommended clinical trials to address the questions identified above. That report was not sent forward from the Public Health Service to the Secretary's office. Instead, in 1983 an ESRD Coordinating Committee was established. The ESRD Coordinating Committee recommended against clinical trials on the grounds that they were not necessary and would be too expensive. They did recommend that FDA establish a registry to track events.

One of the major pursuits of Senator Heinz at the hearing was a demand that the Department undertake rigorous clinical trials. As the witness, I argued that even though there had been an increase from 15 to 65 percent of the Centers which were reusing the dialysis equipment, it was found that there had been no increase in reports of mortality or morbidity. In fact, some literature suggests that there are more untoward events with first use filters than with subsequent use filters. The apparent increase in reuse was probably stimulated by the reimbursement caps effected by HCFA. Interestingly, the price of a dialyzer unit has dropped from the $28 to $30 range to a $10 to $12 range. Reprocessing costs between $7 and $9, so at the present, the cost differential is not great.

FDA labels these devices for single use. But, it has approved reprocessing equipment. There are, however, no guidelines for the use of approved reprocessing equipment. Voluntary standards have been under development by the Association for the Advancement of Medical Instrumentation for several years, but their release continues to be delayed. In any case, they do not address the question of reuse for bloodlines, tubing, the transducer caps, or the transducer filters. Senator Heinz has argued that there should be rigorous standards which are enforced by HCFA. He faults the Public Health Service for not developing such standards. He is well aware that the buck passes from one agency to another with no one accepting responsibility for action. In part, that reflects HCFA's lack of interest in standards because it doesn't have resources for compliance monitoring and enforcement.

Senator Heinz also argues that the reprocessing of filters should be subject to the Good Manufacturing Practices Act. FDA has maintained that the reuse of the filter is a clinical matter and FDA does not regulate or monitor the practice of medicine.

FDA has approved the marketing of two disinfectants which are advertised as being less toxic than formaldehyde. One of these ReNew-D has been implicated in recent outbreaks of bacteremia in which at least one person has died. Two of these outbreaks have been in Florida. One each have occurred in Texas and California. The distributer of ReNew-D, Alcide has withdrawn it from the market.

CDC has investigated a 1983 outbreak in Louisiana in which 27 individuals were affected, 14 of whom died. CDC is investigating the current outbreaks. The question remains unanswered whether this was because of a failure of the disinfectant, or whether it was a matter of improper processing. Although I testified, based on information received from CDC, that they have a standard expressing the adequacy of the use of 4% formaldehyde solution, this is apparently not a formal standard and indeed there are no CDC guidelines for disinfection. We need to have a formal position with respect to which disinfectants are effective, at what strength can they be used, and what are the absolutely essential standards for processing.

In each of the last two issues of the MMWR, CDC has carried articles with respect to dialysis issues. In neither case was the reference to the fact that the Public Health Service was undertaking an assessment. In the first of these, MMWR addressed the issue of exposure to formaldehyde by individuals engaged in reprocessing. Concern among employees of dialysis centers over exposure to formaldehyde is thought to be one of the issues stimulating the use of alternative disinfectants. In last Friday's MMWR, CDC reported on the current outbreaks, with an editorial note calling for more clinical studies. Again, there was no reference to other PHS efforts. Both of these publications will be seized upon by Senator Heinz's staff and used to criticize us.

During my testimony, we reported that HCFA and NIH has established a registry which would make it possible to look at issues affecting reuse. Apparently that information was not correct. There has not yet been a decision as to whether or not the registry will collect information on this issue, or whether it will be analyzed for this purpose.

On June 12 of this year, HCFA participated in a briefing of the Under Secretary prior to a meeting between the Under Secretary and representatives of the dialysis patients organization. A briefing memo from HCFA to the Under Secretary is presently in clearance within the Department.

After the hearing, Dr. Macdonald directed me to carry out an assessment of dialyzer reuse. In the course of carrying out that assessment, it has become evident that communication within the Public Health Service is less than adequate. We uncovered serious omissions and inaccuracies in the testimony which had been prepared based on facts made available last March. Some of these only came to light the day before the comment period for the assessment expired, when we received several hundred pages of information from Senator Heinz. Included in that were internal PHS documents that had not previously been shared with us. On the strength of that, I requested an extension to July 10 for completing our report. However, the recent outbreaks of bacteremia, and additional information that has unfolded from that process, suggest that a report at this time might not be appropriate.

ACTION

The PHS needs to take a clinically and scientifically based stand with respect to this issue. We need to communicate that directly and emphatically to the Health Care Financing Administration, even if that means recognizing that our earlier testimony was flawed.

John E. Marshall, Ph.D.

Item 7

Statements Submitted For Inclusion In This Hearing Record

1. Statement of A. Peter Lundin, M.D., Member, Board of Directors, National Association of Patients on Hemodialysis and Transplantation, and Assistant Professor of Medicine, Downstate Medical Center, State University of New York.

2. Statement of Murray Klavens, Member, Board of Directors, National Association of Patients on Hemodialysis and Transplantation.

3. Statement of Paul Feinsmith, President, National Association of Patients on Hemodialysis and Transplantation.

4. Statement of CD Medical, Inc., Miami, Fla.

5. Statement of Geraldine Biddle, R.N., President, American Nephrology Nurses' Association.

6. Statement of Louis H. Diamond, M.D., President, Renal Physicians Association.

7. Statement of Benjamin Halpren, M.D., President, National Dialysis Association.

8. Statement of Christopher R. Blagg, M.D., Executive Director, Northwest Kidney Center, and Professor of Medicine, University of Washington.

Statement of
Dr. A. Peter Lundin
Assistant Professor of Medicine
Downstate Medical Center
State University of New York
and
Board of Directors of the
National Association of Patients on
Hemodialysis and Transplantation (NAPHT)

As a hemodialysis patient of 20 years and as a practicing nephrologist I am seriously concerned about the reuse of dialysis materials. It appears to me that there are a few major areas which merit attention: 1) safety of using reprocessed materials, 2) the adequacy of reprocessing procedures and 3) coercion of patients into accepting the practice.

The proponents of reprocessing dialyzers and blood tubing have not, in my opinion, convincingly proven that the practice is safe. The data which they present to "prove" the adequacy and safety of reprocessing are gathered under conditions that rarely, if ever bear any relation to the reality of the day to day operation of most dialysis units. Almost all of these studies, moreover, have been carried out by those who have a vested interest in reusing disposable devices. Many of these studies have flaws indicating the potential for unsafe practice. The risks to patients of inadequate dialysis and intoxication from sterilants have not been adequately addressed. This approach is contrary to the scientific method which says that a medical hypothesis can never be proven, only disproven. For patients best interest the obligation is not upon the opponent of reuse to prove it unsafe, but rather for the proponents of reuse to prove that it is not unsafe.

No long-term studies to prove the retained efficacy of dialyzers and their safety have been done under routine day to day working conditions. Studies done in short-term, rarified conditions where acute complications are infrequent are then extrapolated to infer that reuse in any situation is proper.

The greatest dangers to patients from dialyzer and blood tubing reuse are: 1) inadequate dialysis with return of uremic complications and the risk of uremic death; 2) infusion of residual formaldehyde or other sterilants causing hemolysis and possibly other long-term complications (formaldehyde is a known carcinogen); and 3) accumulation in the body of spallated particles from damaged tubing. There are strong reasons to believe that patients subjected to reuse are already being exposed to these and other dangers.

The adequacy of the reused dialyzer is another critical concern. Because of loss of fiber bundle volume due to clotting, the dialyzer will lose effectiveness over time. AAMI standards (which are non-binding and non-enforcible) advise discarding a dialyzer when the efficiency has been reduced to 80% of maximum. Interestingly, indication for discarding a reused dialyzer seems to be changing from loss of fiber bundle volume (quality) to number of times used (economic). The intent seems to be 20-25 reuses regardless of efficacy.

The high-handed manner in which patients are forced to accept the practice of reuse even when they have serious reservations about its safety and quality suggests serious moral and ethical problems. The doctor-patient relationship, in the past the best guarantee of quality medical care, cannot survive a tyranny of one party. Nephrologists, in defense of their own financial security (either as owners or as employees who want to keep their positions) are increasingly basing their dialysis prescriptions on managerial (economic) decisions rather than on the patient's best interest. If patients perceive reuse as being truly for their benefit or at least as safe and effective as single use, it should be easy to persuade the majority of them to acquiesce comfortably. The few who might at first refuse could be won over later, after appreciating the benefits. Compelling patients to consent to reuse with the alternative to seek other arrangements can only arouse suspicion that physicians (or unit managers) have little confidence in their ability, and more importantly, their moral obligation to obtain free consent.

Claims that reuse is cost-saving without compromising safety are increasingly empty. The experience of dialyzer reuse in England is frequently cited as reflective of proper economic concenrs. As the cost of dialyzers has come down the practice in England has decreased. At the same time, reuse has increased in the U.S. As the cost of dialyzers has come closer to the cost of reprocessing, further economic gains from reuse can only be realized by lowering the cost of reprocessing. The effect on quality is easy to forsee.

Steps to correct this situation are, it seems to me, urgently necessary and include:

1) Further studies to ascertain the extent of formaldehyde infusion with reused dialyzers, preservation of adequate dialyzer function under routine day to day operating conditions, long-term safety, and the true cost savings when proper standards of reprocessing are applied. Such studies should apply good scientific method, attempting to prove the proposition that reused dialyzers are not unsafe. That requires that any concerns for safety be answered with unassailable proof. As in the space shuttle disaster disregarded warnings of danger are all too often proven correct at considerable human cost.

2) Adoption on a Federal level of standards of adequacy and a means to enforce them.

3) Informed consent (or right of refusal) for all patients.

I believe that patient safety is widely and seriously compromised by improper prescription of hemodialysis. A prime example of the problem is improper reuse of dialyzers and blood tubing.

Pete. Lund

A. P. Lundin, M.D.
Assistant Professor of Medicine

APL:mmf

Statement of Murray Klavens
Member of the Board of Directors
of the
National Association of Patients on
Hemodialysis and Transplantation (NAPHT)

My name is Murray Klavens and I reside in the town of Plainview, Long Island. I am retired from a career as a physical metallurgist and manufacturer of small high-tech companies. The last years of my working life I was employed by New York State Department of Mental Hygiene, Office of Patient Resources.

My remarks are based on 8 years as treatment partner of my wife who is a home dialysis patient. During these years, I served as NAPHT, Long Island Chapter Chairman for five years, and participant in the Nassau, Suffolk Counties Health System Agency. I also spent five years on the NAPHT Board of Directors and Executive Committee. During that period and continuing to the present I have been Chairman of the NAPHT Technology Committee. For aproximately five years, I served on the AAMI (Association for the Advancement of Medical Instrumentation) Standards Committee for Dialysis and Detoxification. In that capacity I participated in writing dialysis system standards and proposed recommended practices for re-use. I also served as a faculty member on two conferences discussing these problems. I am not making this statement for NAPHT because of the problems of presenting a fully developed policy at this time, but I do base my comments on the knowledge and insights gained during the experiences I have mentioned above.

The question of informed consent is an exceedingly important issue for patients, who are presently intimidated to such an extent that at the moment informed consent, could well be called coerced consent. This intimidation is based on both fact and fancy. The truth is that there are many, if not the majority of dialysis units, where covert and sometimes overt intimidation does occur. Sometimes the patients fear that the result of stories repeated and passed around the patient community. Strengthening this fear is the fact that most patients do not have an alternate place of treatment. The fear is also sometimes strenthened by the treatment which itself involves the patient in a proceedure where he has little or no role or control of what is happening to him. The extent of the intimidation is expressed in the difficulty that exists in trying to get patients to talk to this committee or anyone else about their complaints concerning re-use. In spite of the fact that both oral and written complaints concerning re-use have been made annonymously or under conditions of not revealing names to anyone, the ability to obtain patients to testify or to give statements publicly is limited by the intimidation mentioned above.

For these reasons a first requisite of informed consent is a publicly stated and legally protected and enforced right of refusal. In addition, there must be a full explanation of the possible positive benefits as well as the possible adverse effects of re-use. Such explanations must be specified to be in understandable laymans language.

Since many dialysis centers are operated for profit, and in many cases the physician is a part or full owner of the center, most patients assume cost reduction will mean higher profits and money for the physician. This creates the feeling in the patient that a conflict of interest colors the prescription for treatment procedures and the materials to be used. In the not-for-profit centers, sometimes a similar feeling develops when there is talk of excess funds from dialysis being used to support other hospital functions or excessive perks for administrators. Re-use of dialyzers is not merely a continuation of the dialysis treatment. It is a change in treatment procedure. It supplants a proven process with many years of wide-spread success. In addition, there remain unresolved questions of safety and efficacy and long term effects. The patient therefore should have the right to decline re-use, just as he has the right to decline transplants or CAPD. That right involves saying no without fear of reprisal.

There are scientific studies that indicate that there is a reduction of clearance capability with successive re-uses. For many years manufacturers were pushed to produce dialyzers of higher clearance rates. Now we blithly dismiss the change in clearance rates caused by re-use. The question of middle and large molecule clearances is dismissed as having no importance. It seems that the importance of middle and large molecule clearance are important or unimportant depending upon whichever serves the physicians needs at the moment. At best, we can say that the issue has not been sufficiently researched.

One thing is certain. Dialysis does effect the patients longevity and ability to continue working or participate in community life. There is also evidence that formaldehyde cross links with the proteinacious material deposited on dialyzer membranes during treatment. We do not know the long term effects of this and formaldehyde and other chemical cleanser residues on the patients body. If it turns out that these materials accumulate in human organs as other toxic substances often do, then re-use will really cut the cost of the renal dialysis program by reducing the number of patients requiring long term treatment. They just won't survive.

When we raised the discussion concerning standards we want to be aware of some positive aspects of voluntary and actual standards. AAMI has worked to develop many voluntary standards and has done a fine job in the renal field. It is not easy to obtain the consensus of varied points of view and interests.

The procedures for establishing a national voluntary standard involves extensive discussion and debate as well as several public reviews of the proposed standard. Because such a standard is a consensus statement compromises are necessary before wording of the final product. To the professional the advantages are: his/her freedom of choice in treatment procedures is not curtailed and the opportunity for innovative work exists. Changes in amendments of a voluntary standard is a procedure that can be easily initiated. The strength of a voluntary standard is only that the courts recognize it as a formally accepted practice. The failure to comply with the voluntary standard may be viewed as a violation of normally accepted (medical) practices that leaves the physician open for legal action and damages.

I feel that there is too much latitude for practitioners in voluntary standards. The (sounds like Kaffel and Pacetory) practitioner needs little monitoring, but we don't know how large or small a segement of the dialysis community is represented by such people. Therefore, there is a definite reason for establishing mandatory standards which will specify the safest and most efficacious forms of treatment. Such a standard must not be so rigid that there is no procedure to permit innovation and change. There must be provision for amendment to include new knowledge and experience. The overall picture of dialysis shows some glowing contradictions concerning re-use. The manufacture of new, first use materials is bound and controlled by rigid procedures, standards and FDA Good Manufacturing Practices (GMP's). Many are mandated by government agencies, and are intended to guarantee safety and performance of the product. The re-manufacture for reuse is not required to meet these conditions. This would seem to be a giving up of the need to protect the patient. If the reprocessor had to meet the conditions of first-use production, then re-use would no longer be attractive economically and would come to a screeching halt.

In closing, I wish to state once again that the ability of the patient to feel free to refuse a form of treatment is an absolute right that must be maintained, not only for dialysis patients, but in many other chronic illnesses as well. Thank you.

NAPHT
NATIONAL ASSOCIATION OF PATIENTS ON
HEMODIALYSIS AND TRANSPLANTATION, INC

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My name is Paul Feinsmith. I am the current President of the National Association of Patients on Hemodialysis and Transplantation(NAPHT). NAPHT was founded in 1969 by six patients at Downstate Medical Center in Brooklyn who were undergoing what was then experimental treatment for kidney failure. Today NAPHT is the largest organization of all kidney patients in the country and this is one of many appearances at Congressional testimony we have been privileged to make.

I am a lawyer in private practice in Ft. Lauderdale Florida. I work full time, am married and have three children. In addition to my responsibilities at home, at work, and with NAPHT, I am very involved with the Kidney Foundation on a local and national basis. I have been on home hemodialysis for fourteen years. In short, I am the success story that the Federal commitment to ESRD is all about. But I have come here today to speak for the membership of NAPHT and for all kidney patients about some issues that are of great concern to us.

When the Federal government made the commmitment to provide renal replacement therapy to all citizens a tremendous burden was lifted from patients, their families, and the professionals who cared for them. No one dared dream that what Dr. Belding Scribner of Seattle called "a noble experiment" would turn into a program that spends about two billion dollars of the government's money and gave birth to a multi-million dollar industry. In the years since 1972 much has changed in the way care is delivered.

One of the biggest changes has come in the reuse of disposable hemodialysis equipment. In the early days of dialytic therapy re-use was practiced on a routine basis due to the scarcity of resources. However, since the implementation of the prospective payment system, in 1983, about 60% of patients are being subject to the reuse of dialyzers, lines,and in some cases transducer filters. The reason given to patients for this practice is the change in reimbursement methods. Patients are being told that the only way dialysis centers can stay in business is to re-use.

Why is NAPHT concerned? Since 1983 we have received three times the number of complaints regarding facilities and the type of care being delivered. Many of these complaints arrive unsigned or with disclaimers from the patients asking us not to reveal their identity because they are afraid of what may happen to them when they go for dialysis if it becomes known that they have complained.

And what is the nature of these complaints? Patients have not been well informed about re-use. In many cases patients have been told that a facility is beginning reuse and no options are presented to the patients. There is certainly no informed consent available to the majority of patients who are being subjected to reuse. Many patients complain that they are being told to go elsewhere if they do not like or want reused dialyzers. In many areas of the country however, there simply is no elsewhere as one or two companies have a monopoly in a particular area and therefore all the facilities practice reuse.

Many patients have little understanding of the reuse process. They are ill informed as to the parameters for reusing a dialyzer.Many patients are under the impression that the only criteria for reuse is how much money is being saved. Many patients complain that since the introduction of reuse they have more frequent need for blood transfusions. Many say they need twice or three times the amount of anticoagulation on a reused dialyzer and say they experience frequent nose bleeds and excessive bleeding from their fistula needle sites.

We are also concerned about the lack of clinical trials that have been done in this area. We would hate to think that we will have to wait to see increased levels of morbidity and mortality related to this procedure. We believe that if reuse is to be done it must be done properly with attention paid to the safety of both staff and patients. As we have already mentioned we have heard of many facilities which improperly and unsafely perform this procedure. We have made a major contribution to the proposed AAMI Standards on reuse of Hemodialyzers. Chief among these is that the number of times a dialyzer is used not be the criteria for determining whether a dialyzer can be used again.

We hear from patients that basic amenities such as clean linens with each treatment, adequate amounts of band-aids and gauze dressings are not being provided. There has also been a change in staffing patterns of dialysis units with a reduction in the number of registered nurses hired over non-licensed personnel. You have only to ask our colleagues from the American Nephrology Nurses Association about this issue. We urge you to consult with social workers and nutritionists to find out about the increase in their case loads over the last two years. And we ask you to look closely at where money being saved is going.

We are also concerned with other issues besides reuse of disposable devices. We have read with great dismay the reports in the press regarding organ transplantation and the purported existence of black marketeering of organs. We are deeply distressed about the alleged priority given to foreign nationals for transplantation which seemed to be based solely on the ability to pay. We testify to the need for a national system for organ sharing as well as the establishment of a network to track non-renal transplantation. Specifically, we urge that the ESRD Networks be used to track non-renal transplants. We feel it would be a foolish expenditure to "reinvent the wheel" and create a new agency to do exactly what the ESRD Networks do.

In summary, NAPHT believes that if reuse is to be done it must be done with particular attention to safety and consent of patients. We urge this Committee to propose legislative and or regulatory relief such as that contained in the AAMI Guidelines that would guarantee this. Further, we urge that the ESRD Networks be given the enforcement power to assure strict adherence to safety and quality issues.

NAPHT is an organization that was founded by people dedicated to meeting an urgent need: the preservation of their lives and those of others like them. NAPHT is grateful for the opportunity to let the public know that we intend to insure that all modes of renal replacement therapy remain available to all who desire them, and that such therapies are safe and of a uniformly high quality, regardless of the socio-economic status of the patient.

SUMMARY COMMENTS REGARDING REUSE OF DIALYZERS AND OTHER DIALYSIS SUPPLIES PRESENTED TO THE SENATE SPECIAL COMMITTEE ON AGING BY CD MEDICAL, INC., MIAMI, FLORIDA

CD Medical, Inc., (formerly Cordis Dow) has constantly and forcefully stated that the patient treated with remanufactured dialyzers by health care providers is entitled to the same assurance of quality, function, cleanliness, nontoxicity, nonpyrogenicity and sterility as that provided by new, single-use dialyzers.

These assurances cannot adequately be achieved using dialyzer remanufacturing procedures as presently practiced. In 1982-83, dialyzer reuse was practiced on about 20 percent of all patients. Today that figure is over 60 percent. There are perhaps 500 or more different procedures used today for remanufacturing of dialyzers by the clinics. These remanufacturing procedures are, in the main, completely uncontrolled by regulatory agencies. State control is minimal and ineffective.

In order to properly remanufacture or reprocess dialysis supplies, a facility must have a functioning quality assurance program. A minimum quality assurance program includes the following:

Adequate organizational structure and sufficiently trained personnel with appropriate education;

All significant changes in process or testing must be statistically validated;

Quality review of all production records including components, manufacturing materials, inprocess materials, packaging materials, labeling, and finished devices;

Verification that quality problems are identified, documented, and corrected;

Planned and periodic audits by the quality system with documented reports reviewed by management; and

Maintenance of files of written and oral complaints about device performance, quality, safety, durability, or effectiveness and records of the resolution of each complaint.

There are many technical and safety issues involved in reuse of dialysis supplies. A partial list includes:

A. Sterility of Remanufactured Devices

Dialysis supplies are disinfected, not sterilized.

Is any microbial condition other than sterility appropriate for reused devices? Many types of microorganisms, and often very small quantities of them, are capable of causing bacteremias, septicemic conditions and other undesirable infections. This is particularly true in health care facilities and with debilitated patients.

B. Toxicity of Remanufactured Devices

Cleaning and washing methods, disinfectant use, packaging, aging, exposure to heat and light, etc., may affect the finished remanufactured device.

C. Pyrogenicity of Remanufactured Devices

Many bacteria capable of generating endotoxins survive and grow under extreme conditions of temperature and pH and with minimum nutrient requirements. Pyrogen tests must be performed on remanufactured devices.

D. Biocompatibility of Remanufactured Devices

Has the biocompatibility of the device changed during remanufacturing? This is a very important consideration for products that come in contact with body fluids such as blood.

E. Function and Effectiveness of Remanufactured Devices

F. Physical State of Remanufactured Devices

Factors such as tensile strength, burst pressure, leak pressure, etc., must be considered.

G. Workplace Hazards Created by Reuse Disinfectants

It is obvious, based on all known facts at present, that reuse of dialysis supplies has not been proven safe and efficacious. Well-controlled studies for moderate and long-term use of remanufactured products have not been done.

Informed consent or choice of being treated with a new dialyzer should be offered to the patient.

Remanufacturing or reprocessing is definitely part of the description of the "manufacturer" as defined in The Federal Food, Drug and Cosmetic Act and Good Manufacturing Practices regulations.

Until all clinics are required to follow adequate and appropriate Federal Standards and Regulations with respect to reuse and are inspected for compliance, a "so-called" double standard will continue and patient care will continue to be compromised.

ANNA
American Nephrology Nurses' Association

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March 14, 1986

Senator H. John Heinz
Chairman, Senate Special Committee on Aging
G-33 Dirksen Senate Office Building
Washington, D.C. 20510

Dear Mr. Chairman:

The American Nephrology Nurses' Association represents over 3000 registered professional nurses involved in the delivery of care to patients with renal disease. The majority of our members (65%) are employed in hemodialysis units.

We have read the Staff Report of the Senate Special Committee on Aging, "Issues in Reuse of Kidney Dialysis Devices: Is Reuse Abuse?" and would like to have our comments included in the record of the hearing on this issue that you convened on March 6, 1986.

We believe the report contains many sweeping, absolute and general statements which could be easily refuted. There are nurses in dialysis centers all over the United States who function as patient advocates, believing in informed consent, patients' freedom of choice, and safeguarding quality of care in all areas, including reuse. We take no issue, however, with the "Problems Associated with Reuse" as outlined in the report. If these problems occur once, it is once too often.

We wholeheartedly support the Staff Recommendations included in the staff report with the exception of Recommendations 2 and 3. We would like to address these individually.

Recommendation #2:"The DHHS should withhold issuance of its proposal to establish lower composite rates for dialysis services (which assume reuse) until the safety and efficacy of reuse is determined." It is well known and accepted that prospective payment systems lead providers to choose the lowest cost situation. Therefore, the incentive for reuse exists in the hemodialysis industry today. Further changes in the reimbursement rate are not likely to alter that incentive in any way.

ANNA National Office
North Woodbury Road / Box 56, Pitman, New Jersey 08071
Telephone: 609-589-2187

Recommendation #3: "If DHHS continues to allow individual physicians and clinics to decide whether or not to reuse, it should establish a two-tiered reimbursement system for dialysis facilities to reflect the difference in the cost between facilities that reuse devices and those that do not reuse. This will save money paid for excessive profits at reusing facilities, while it will avoid putting undue pressure to reuse on physicians and clinics that have decided reuse is unsafe or less effective."

We believe it is premature to suggest a two-tiered reimbursement structure until the results of the studies called for in Recommendation #1 are reported. At that time, if the reuse procedure is deemed safe and efficacious such a strategy might be considered. If it is not found to be so, reuse will not be practiced and addressing reimbursement will not be necessary.

In the meantime, we feel a move such as suggested in this third recommendation might be of more harm to patients than safely conducted reuse/reprocessing of dialyzers. The two most costly components of a dialysis treatment are supplies (the artificial kidney being the most expensive supply) and personnel costs (registered nurses being the most expensive category of personnel). If a facility that is currently practicing reuse (whether they are making "excessive profits" from the procedure or not) suddenly receives a lower reimbursement rate we fear that the result will be a reduction in the number of professional staff, namely registered nurses, available to plan, implement, assess, and evaluate the care the patients receive. We have grave concerns about the impact that would have on the individual patients and on the ESRD program as a whole, as "sicker" patients are "costlier" patients. Your actions, then, would have a negative impact on the patients you are now trying to protect and the program you are trying to preserve.

We urge the Committee to carefully consider excluding Recommendations 2 and 3 from any further actions they may take on this matter. We appreciate this opportunity to share our concerns with you and stand ready to assist the Committee in any way on this or any other issue of concern to the ESRD program or its beneficiaries.

Sincerely,

Geraldine Biddle

Geraldine Biddle, RN
President

rpa
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✓

April 1, 1986

Honorable John Heinz
Chairman
Special Committee on Aging
Dirksen Senate Office Building
Room G-33
United States Senate

Dear Senator Heinz:

It is a pleasure to have the opportunity of filing with the Committee preliminary comments on the issue of reuse of dialyzers on behalf of the Renal Physicians Association (RPA). Please include this letter in the formal record of the Committee's March 6, 1986, hearing on this subject.

RPA is a national organization, representing 1,200 physicians nationwide involved in the care of patients with kidney disease. RPA members are the physicians responsible for administering dialysis therapy and for assuring that this practice is both safe and efficacious. As such, RPA has taken an active role in the issues surrounding reuse of dialyzers. A number of our members, including several current and past board members, have conducted scientific studies and surveys addressing the questions currently being considered by the Aging Committee. RPA has sponsored national surveys and both national and international conferences covering the various aspects of dialyzer reuse. These included safety and efficacy, as well as the ethical, legal, and cost implications of reuse of dialyzers.

Because of the history of RPA's past and present involvement with the reuse issue, we are disappointed that the Association was not permitted to testify before the Committee at its recent hearing on this issue. RPA believes expert opinion from both the public sector and medical community is essential in any approach taken on this issue and we look forward to actively assisting the Committee in its consideration of dialyzer reuse. We intend to convene a panel of experts to consolidate the information already developed covering the various issues of concern to your Committee, and plan to finalize a report within the next 90 days. During our deliberations, we will consult with various officials of government, at the Health Care Financing Administration, the Public Health Service and the Food and Drug Administration. We would obviously be pleased to work with the Committee and staff on this as well.

✓

A few brief comments might be in order at this time. On the issue of safety, there is abundant scientific and verifiable data to support the contention that the reuse of dialyzers, utilizing the standard procedures and existing guidelines, is both safe and efficacious. The RPA will provide your Committee with an analysis, appropriately referenced, supporting this

Renal Physicians Association • 1101 Vermont Ave., NW, Suite 500 • Washington, DC 20005-3457 • (202) 898-1562

contention. There is at this time, no body of scientific opinion that contends that reuse of dialyzers, undertaken following the appropriate guidelines, is dangerous to the patient's health. In fact, under the ESRD program, the states conduct annual on-site surveys to evaluate dailysis unit performance in providing quality patient care services.

Guidelines for reuse practice have been issued by the National Kidney Foundation (NKF), and a number of End Stage Renal Disease program network organizations. The Association for the Advancement of Medical Instrumentation (AAMI), with input from a wide range of experts in the field, has issued extensive draft guidelines.

In summary, RPA is looking forward to working with you and your Committee during your deliberations over the next months. We will issue a report covering the safety and efficacy of dialyzer reuse, and will be endorsing guidelines for practice.

Sincerely,

Louis H Diamond

Louis H. Diamond, MD
President

cc: Members, Committee on Aging
LHD/dmm
G-RT-0057

National
Dialysis
Association

WRITTEN TESTIMONY FROM
BENJAMIN HALPREN, M.D, PRESIDENT
NATIONAL DIALYSIS ASSOCIATION
TO THE SENATE SELECT COMMITTEE ON AGING
IN RESPONSE TO THE HEARINGS ON
REUSE OF DIALYSIS DEVICES
MARCH 6, 1986

INTRODUCTION

The National Dialysis Association (NDA) is a voluntary, membership organization representing dialysis facilities of all types on national issues. The NDA was established in December, 1985, and represents 80 dialysis facilities. The organization is governed by a 20-member board of directors composed of one medical director and administrator from each of the ten HCFA regions.

COMMENTS

The National Dialysis Association would like to offer our comments on several issues addressed during the hearing. However, before I begin these comments, I would like to express our strong disappointment at the committee's one-sided presentation on the reuse issue. The committee did not seem interested in hearing testimony from patients or facilities who support the practice of reuse.

Many of the dialysis facilities which practice reuse follow guidelines developed by the Association for the Advancement of Medical Instrumentation (AAMI), state government regulators or the National Kidney Foundation. There are also a large number of patients who prefer to reuse because of their experience with first-use syndrome and other complications. In fact, recent National Institutes of Health (NIH) studies confirm the presence of mortality with the first-use syndrome and there is yet to be reported mortality from dialyzer reuse. With due respect, I think this committee could have made the suggestions presented in the committee report and still have heard both sides of the reuse issue.

It is the position of the NDA board of directors that if a dialysis facility practices dialyzer reuse then there should be standards for that facility to follow. The practice of reuse can be done safely and this should be encouraged. The NDA will support the development of federal minimum reuse standards as long as they are reasonable.

Standards have already been developed and are followed by many facilities in the dialysis community. We recommend that these standards be carefully examined and considered if federal standards are promulgated.

The National Dialysis Association supports quality care for patients on dialysis and condemns any activity that would threaten dialysis patients.

It is the position of the NDA board of directors that we be involved in the process of any development of federal regulations. As representatives of dialysis facilities we are able to voice the concerns and views of all personnel in a dialysis facility, i.e. nurses, administrators, technicians and patients.

Thank you for the opportunity to present the views of the National Dialysis Association. For more information please contact:

Bianca DeLille
National Dialysis Association
1615 M Street, N.W.
Suite 220
Washington, D.C. 20036
(202) 887-0906

NORTHWEST KIDNEY CENTER
700 BROADWAY • SEATTLE, WASHINGTON 98122 • (206) 292-2771

March 13, 1986 NKC-86-0397

Senator John Heinz
Chairman
Senate Select Committee on Aging
277 Russel Senate Office Bldg.
Washington, DC 20510

ATTN: Mr. Cunningham

Dear Senator Heinz:

Dr. Belding Scribner, Professor of Medicine at the University of Washington, and I would like to submit the following with regard to your committee's recent hearing on disposable dialyzer devices.

In the United States the technique for dialyzer reuse was first developed at the University of Washington, Seattle, in 1966. At that time, patients used Kiil nondisposable dialyzers, and when a technique was developed to return almost all the residual blood from the dialyzer to the patient, it became possible to clean the dialyzer and disinfect it with formaldehyde for reuse. Motivation for this was to save the patient's time and effort. Many of the dialysis patients in Washington State were using home hemodialysis, and patient and family devoted considerable time to rebuilding and disinfecting the dialyzer before each dialysis. With the Kiil dialyzer, there was an appreciable incidence of leakage when the dialyzer was tested prior to disinfection; if this occurred, the dialyzer had to be disassembled and rebuilt. Reuse reduced the need to rebuild the dialyzer as frequently, and patients were trained to reuse for up to six dialyses.

With the availability of presterilized, disposable dialyzers, time saving ceased to be a major factor, but cost of the dialyzer became important, particularly prior to the Medicare End-Stage Renal Disease (ESRD) Program in 1973. Techniques were developed for reuse of both disposable flat plate and hollow fiber dialyzers for patients on home dialysis. These techniques, while modified with time, have been in continuous use in the Northwest Kidney Center's home dialysis program since 1967, and about half our home dialysis patients continue to reuse their dialyzers.

With the Medicare ESRD Program and relatively generous reimbursement for outpatient dialysis in the 1970's, reuse was not necessary in our facilities. We continued reuse in our home dialysis program as this helped to conserve state funds used to support home dialysis patients at a time when Medicare reimbursement was inadequate for home dialysis.

Senator John Heinz, Chairman
Senate Select Committee on Aging
March 13, 1986
Page 2

With introduction of composite rate reimbursement in 1983 and consequent pressure to reduce costs in facilities, we now reuse dialyzers in our facilities--approximately 75% of the more than 200 patients dialyzing here utilize reused dialyzers. Processing is done with an automated machine in our main facility and by hand in one of our satellite facilities, and strict control of the process is maintained. We have never seen a significant problem that could be blamed on dialyzer reuse, and we believe that carried out appropriately, this is a safe procedure which reduces the cost of treatment. It also has been shown to have benefits for patients in avoidance of the "first-use syndrome" and related complications and a lower incidence of blood leaks. We believe there is sufficient documentation in the medical literature to demonstrate these points. We support the proposed "Recommended Directions for Reuse of Hemodialyzers" to be published by the Association for the Advancement of Medical Instrumentation in the near future.

There remains one issue which is more difficult--the question of whether reuse may have any long-term effects--either beneficial or detrimental. More than 2,000 patients have been treated in the Northwest Kidney Center program over the last 25 years without any obvious long-term complications we believe could be ascribed to dialyzer reuse. However, this is a relatively small patient population. With recent interest in the effects of membranes on blood proteins there is also the possibility that long-term reuse could be beneficial to patients. Questions like this can only be answered by adequate data on a large number of patients and by prospective studies. Such data on dialysis patients is not available in the United States, in contrast to Europe, Canada, Australia and New Zealand. Only with a national ESRD data system and with the cooperation of the National Institutes of Health will it be possible to answer this and similare questions.

With this in mind, we wish to draw attention to a recent position paper discussing the need for a national ESRD registry (Attachment 1). We urge the committee in its findings to consider the need for a national ESRD registry, whatever the committee's ultimate position may prove to be on dialyzer reuse. Clearly, we believe dialyzer reuse to be a safe procedure, but the best way of finally proving or disproving this will depend on the availability of appropriate data.

We would be happy to talk further to you or your staff if you so wish.

Sincerely yours,

Christopher R. Blagg, M.D.
Executive Director, Northwest Kidney Center
Professor of Medicine, University of Washington

CRB:mjs
cc: Senator Daniel J. Evans
Senator Slade Gorton

ATTACHMENT I

POSITION PAPER
MEETING TO CONSIDER THE ESTABLISHMENT OF A
NATIONWIDE ESRD PATIENT DATA SYSTEM
Washington, DC
July 19, 1985
1:00 p.m.-4:30 p.m.

PARTICIPANTS

Steven R. Alexander, M.D.; Pediatric Nephrologist, Oregon Health Sciences University, Portland, Oregon; Chairman, Ad Hoc Executive Committee, North American Pediatric ESRD Cooperative Study.

Benjamin A. Barnes, M.D.; Director, New England Organ Bank, Boston, Massachusetts; Representative of the American Society of Transplant Surgeons.

Christopher R. Blagg, M.D.; Executive Director, Northwest Kidney Center; Seattle, Washington; Professor of Medicine, University of Washington, Seattle, Washington; Counselor, Renal Physicians Association.

John D. Bower, M.D.; Professor of Medicine, University of Mississippi Medical Center, Jackson, Mississippi; President, Renal Physicians Association.

Dominick E. Gentile, M.D.; St. Joseph's Hospital Renal Center, Orange, California; Former President, ESRD Forum of Networks.

Gladys Hirschman, M.D.; Chronic Renal Disease Program Director, DKUH, NIADDK, National Institutes of Health, Bethesda, Maryland.

Henry Krakauer, M.D., Ph.D.; Health Care Financing Administration, Baltimore, Maryland; National Institutes of Health, Bethesda, Maryland.

Karl D. Nolph, M.D.; Professor of Medicine and Director of Division of Nephrology, University of Missouri, Columbia, Missouri; Director, Clinical Coordinating Center of the NIH CAPD Registry.

William Pfaff, M.D.; Professor of Surgery, University of Florida, Gainesville, Florida; President, ESRD Forum of Networks.

Richard Glassock, M.D.; Professor of Medicine, University of California-Los Angeles; Representing the National Kidney Foundation, was unable to be present.

PURPOSE OF THE MEETING

To discuss the development of a national end-stage renal disease (ESRD) patient and treatment registry and the means by which this may be undertaken.

REASONS FOR CALLING THE MEETING AT THIS TIME

With the institution of the Medicare ESRD program 12 years ago, the very successful NIH/ACS Transplant Registry and the NIH Dialysis Registry were replaced by an ESRD Medical Information System, originally directed by the Bureau of Quality Assurance. The history of the ESRD data system has been fraught with problems, both outside and inside HCFA. Despite the accumulation of large quantities of data by HCFA, it is only in the last two years, with the help of the ESRD Networks, and in particular during the last year with the aid of specifically interested HCFA staff, that reliable analyses, other than purely demographic information, have become available.

A number of factors make this a propitious time to reexamine the development of a patient registry:

1. During the last year the utility of the HCFA data to answer questions with regard to transplantation has been clearly demonstrated. The data base includes some 95% of current transplants, and is 90% compliant in terms of information regarding transplantation and follow-up, primarily because of recent efforts by the American Society of Transplant Surgeons. Nevertheless, there is concern that the HCFA staff working with the ESRD data system require continuing advice and direction as to analysis of the data.

2. NIH currently funds the National CAPD Registry, which follows approximately two-thirds of the CAPD patients in this country. This registry, utilizing the University of Missouri as clinical coordinating center and the EMMES Corporation as data coordinating center, has proved very successful. Nevertheless, a question remains as to how long NIH will continue to fund this. A comprehensive national ESRD registry would extend the CAPD Registry to all CAPD patients and provide more complete data on pre- and post-CAPD events. The relative success of the CAPD Registry highlights the lack of comparable information on other modalities of dialysis which account for more than 85% of the dialyses performed in the United States.

3. A recent poll of the American Society of Pediatric Nephrology showed that pediatric nephrologists in the United States and Canada are overwhelmingly in favor of developing a pediatric registry because of the specific problems affecting their patients. Recently an application has been submitted for an NIH contract to fund a cooperative study to establish a North American Pediatric ESRD Registry to address these special information needs.

4. NIH recently has become more interested in support of clinical research in end-stage renal disease and may be very open to establishment of an ESRD patient registry which could provide reliable data on all modalities of dialysis and transplantation. A recent meeting sponsored by HCFA discussed topics for future ESRD

research, and a registry was seen as essential in developing special studies related to the treatment of both adult and pediatric ESRD patients, in addition to collecting ongoing clinical information.

5. The ESRD Networks have become agents for validation of medical information submitted to HCFA and serve to communicate with local facilities in securing data. Their current role in securing data from the provider is a critical point in achieving usable data. Were the Networks to be discontinued, it would be necessary to replace this function, with uncertainty as to both product and expense.

6. The recent transplant legislation requires the Transplant Task Force to include in its considerations development of a transplant registry. It is generally agreed that a transplant registry should be part of a comprehensive ESRD registry because patients shift between different modalities of treatment. The American Society of Transplant Physicians has also expressed its interest in working towards such a registry.

7. Fragmentation of the data available into different data systems is illogical and wasteful, and the mass of data in HCFA cannot be fully utilized without outside direction because HCFA is not constituted to be responsive to the clinical data needs required for rational management of a national ESRD program.

8. It would almost certainly be possible to establish a national ESRD patient registry without significant increase in the total cost to HCFA and NIH for the existing system, the CAPD Registry and the proposed pediatric and transplant registries.

AREAS OF IMPORTANCE

1. Collection and Validation of Data

HCFA already has a large body of data, and it is important to continue to use the billing system and the existing forms as the primary source of information. Nevertheless, there is need for better validation and correction of the data, and this should not be the direct responsibility of HCFA. The Networks' existing role in relating to local facilities has been helpful in generating data, and they could continue this if so directed. The imposition of sanctions by reducing reimbursement as a penalty for noncompliance in a national ESRD data system exists, but so far has not been used.

2. National Institutes of Health

There is need for access to reliable data on ESRD patients to identify areas for clinical research. There is need for a mechanism to collect data for special studies that may be developed to answer specific questions, and these studies may be designed more economically in many instances by using purposively selected samples of the patient population. Such selection, to permit national generalization of conclusions, must be based on a total national patient registry.

3. Health Care Financing Administration

HCFA staff need advice and guidance in biomedical and biostatistical areas, particularly in specifying data needs, developing instruments for data collection, and developing techniques for data analysis to serve the needs of both HCFA and NIH. This observation is not a criticism of the HCFA record, but is the recognition that HCFA was not authorized as a source of clinically relevant data in its commitment to financing patient care.

4. Collaboration

A national data registry would require collaboration of HCFA and NIH at the working level, with the official approval and direct involvement of Dr. Regina McPhillips, Director, Bureau of Data Management, HCFA, and Dr. Gary Striker, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIADDKD, NIH. There is also need for community collaboration, and this will require reestablishment of confidence in the nephrology community. This will require cooperation of the major specialty organizations and a speedy return of useful data to facilities once the registry is established.

5. Funding

Data collection and analysis is already carried out by HCFA, which also funds the Networks which do some data validation. Funding would be required from NIH for a steering and planning committee and a coordinating center. The total cost of the basic registry will not likely exceed the cost of the various present systems and the proposed transplant and pediatric systems. Extra costs associated with special studies would be the responsibility of the NIH.

Outside support could also be sought from industry, professional societies, and possibly from facilities.

6. Steering and Planning Committee

The Steering and Planning Committee would include appropriate professional representation. The committee could be nominated by the appropriate professional societies.

The roles of the Steering and Planning Committee would include, but would not necessarily be limited to the following:

* Idenfication of major issues to be addressed by the registry.
* Assessment of the impact of current and emerging medical procedures for the management of patients with end-stage renal disease.
* Provision of guidance on the approaches to be used in data collection.
* To appoint working groups drawn from its own membership, with additional expertise as needed, to develop plans and address specific issues within the limits of the registry.

These important issues must have substantial input from clinicians. The ultimate success of the registry will depend on the leadership and involvement of the Steering and Planning Committee so that the registry develops credibility with the whole ESRD community.

It is anticipated the Steering and Planning Committee would meet twice yearly when the registry is in stable operating mode, but initially would meet more frequently. It might choose to appoint a smaller executive committee to handle ongoing questions and issues.

NIH would be responsible for sponsoring the operation of a Steering and Planning Committee and will provide biomedical and biostatistical expertise as necessary to develop and implement the national ESRD patient registry. NIH will also sponsor other additional expertise as needed.

7. Health Care Financing Administration

HCFA would be responsible for collaborating with the Coordinating Center in revision of existing data collection instruments and devising new forms to secure compatibility of all forms with the existing data system. They would be responsible for the acquisition of data, the distribution of forms, and the integration of current data management and validation procedures and any future changes in these. They would create data suitable for analysis and would collaborate with the Coordinating Center in carrying out analyses.

8. Coordinating Center

The responsibilities of the Coordinating Center, in collaboration with the HCFA and NIH, would include: reviewing existing data collection instruments and helping to devise new forms, as required; ensuring data reporting compliance; designing observational studies to be implemented by the registry as instructed by the Steering and Planning Committee; designing analytical procedures; and analyzing of the data. The Coordinating Center would require clinical guidance from the Steering and Planning Committee and the assistance of a systems specialist experienced in design and methodology and of a statistician(s) experienced in the analysis of both statistical and economic data.

9. Registry Oversight Committee

Membership of this would be selected by the Steering and Planning Committee, NIH, and HCFA, and could include representatives from the Steering and Planning Committee. Its responsibility would be to review and advise on the activities of the Coordinating Center, to identify problems and to recommend appropriate actions. It would be a committee external to and independent of the Coordinating Center. Such a committee would meet initially twice a year and yearly thereafter.

10. Subcommittees

The Steering and Planning Committee would be empowered to appoint other subcommittees, such as a subcommittee on pediatric ESRD, as required.

THE END PRODUCT OF THE REGISTRY

1. To describe the distribution, demographic attributes, ESRD diseases, and geographic residence of patients across the several modalities of ESRD treatment and the serial changes over time.

2. To provide appropriate selected national samples of patients to permit clinical studies leading to conclusions that may be generalized for national policy formulation.

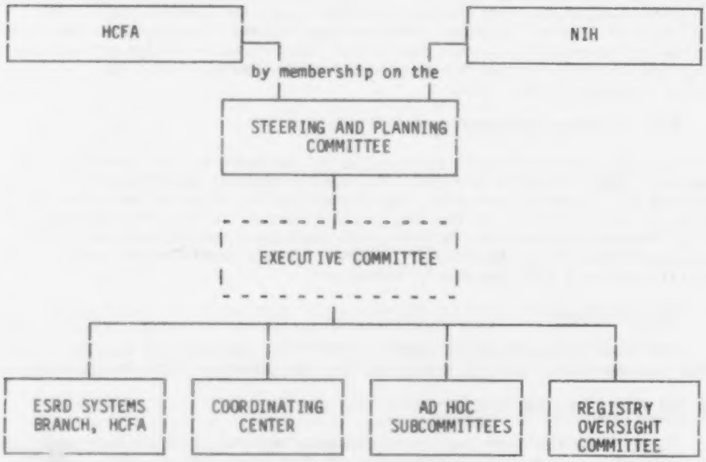
3. To identify what modalities of treatment are best suited to which patients, and to compare the medical efficacy of various treatments and survival analyses.

4. To identify the economic or fiscal impacts of alternative modalities of treatment, their cost-effectiveness and their broad socioeconomic impact, and to analyze data to permit rational allocation of resources in the treatment of end-stage renal disease based on the relative merits of the available modalities of treatment.

121985

Position Paper
Meeting to Consider the Establishment
of a Nationwide ESRD Patient Data System
July 19, 1985
Page 7

PROPOSED STRUCTURE


HCFA
NIH
by membership on the
STEERING AND PLANNING COMMITTEE
EXECUTIVE COMMITTEE
ESRD SYSTEMS BRANCH, HCFA
COORDINATING CENTER
AD HOC SUBCOMMITTEES
REGISTRY OVERSIGHT COMMITTEE

CRB:mjs
121985

Item 8

Research Papers Submitted For Inclusion In This Hearing Record

1. Repeated Use of Dialyzers is Safe: Long-Term Observations on Morbidity and Mortality in Patients with End-Stage Renal Disease, 1986.

2. Mortality and morbidity of reusing dialysers, 1978.

3. National Kidney Foundation Revised Standards For Reuse Of Hemodialyzers, December 2, 1983.

4. Dialyzer Membranes: Syndromes Associated With First Use, and Effects Of Multiple Use, undated.

5. Hemodialyzer Reuse In End-Stage Renal Disease Network 7: Assessment of current practices, revised Network 7 standards and recommendations for compliance, May 1985.

Nephron *42:* 217–223 (1986)

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Repeated Use of Dialyzers is Safe: Long-Term Observations on Morbidity and Mortality in Patients with End-Stage Renal Disease

Victor E. Pollak, K. Shashi Kant, Sandra L. Parnell, Nathan W. Levin

Dialysis Clinic, Cincinnati, and Division of Nephrology Department of Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio, USA; Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Mich. USA

Key Words. End-stage renal disease · Multiple dialyzer use · Morbidity · Mortality

Abstract. In treating patients with end-stage renal disease, the dialyzer may be used on multiple occasions rather than once. Long-term effects of this practice are unknown. We report 259 and 1,059 successive patients from facilities practicing reuse in Cincinnati and Detroit, followed, respectively, for 535 and 2,209 patient years. The morbidity was relatively low, expressed by the number of hospital admissions (1.63 and 2.19/year) and by days in hospital (14.24 and 22.71/year), respectively. In Cincinnati the unadjusted case fatality rate was 70% of that in the Ohio Valley Renal Disease Network, in Detroit it was 96% of that in the Michigan Renal Network. There were no adverse long-term effects of multiple use of dialyzers.

Introduction

Patients with chronic renal failure have been treated by chronic hemodialysis for over 20 years. Many factors determine the treatment prescribed. As treatment is expensive, containment of cost is important for the facility that takes care of the patients, and to those responsible for payment of costs.

One major element of cost is the dialyzer. To contain costs the practice of multiple use of dialyzers, shown to be safe in 1964 [1], has become widespread [2–5]. Because of concern about its safety we analyzed the events in a dialysis unit over a 15-month period and showed that, in this short-term sense, the multiple use of dialyzers was safe and effective [4]. Others have come to similar conclusions [2, 5]. There is now clear evidence that more symptoms occur during dialysis with the first than with the subsequent use of dialyzers [6, 7].

Whether the practice of dialysis using dialyzers on multiple occasions is associated with adverse long-term effects is unknown. To address this question we analyzed and here report patient outcomes in two geographically separated dialysis units that have practiced the multiple use of dialyzers over 6½- and 12-year periods.

Methods

Patients were selected for end-stage renal disease (ESRD) treatment by selection committees at the University of Cincinnati Medical Center (UCMC) and Henry Ford Hospital (HFH). Liberal criteria were used. The characteristics of the UCMC patient population have been described in detail [8]. Cincinnati patients whose condition stabilized were transferred for chronic maintenance dialysis to the Dialysis Clinic Cincinnati (DCC), a 'free-standing' dialysis unit affiliated with UCMC; Detroit patients were transferred to three satellite HFH outpatient units. Some patients were first dialyzed elsewhere and were later transferred for chronic maintenance dialysis. During the study period, all patients were treated by the same physicians. DCC opened in July 1977; by July 1978, virtually all Cincinnati patients requiring chronic maintenance dialysis were treated at DCC, at least for the vast majority of their treatments. This practice has continued. Over the years >80%, and at present >89%, of all outpatient dialyses in patients with ESRD were done in the limited care setting. With the exception of sick patients requiring more intensive care, all HFH patients were transferred to outpatient units. In Detroit, about 90% of the total patient population were in the satellite units at any one time.

At DCC the patients are cared for during hemodialysis treatments by trained patient care technicians under the immediate supervision of nurses. At HFH the patients are cared for by nurses or clinical technicians under nursing direction. In both centers each patient is visited during each dialysis session by a nephrologist member of the Division of Nephrology. On admission to hospital

(UCMC or HFH) the patient is cared for by the nephrologist, with assistance where needed from physicians in other disciplines. With few exceptions all surgical procedures including vascular access procedures are done by surgeon members of the Divisions of Transplant Surgery.

Treatment Duration

The objective of this study was to determine the outcome in patients treated with the multiple use of dialyzers. In Cincinnati dialyzers are used only once at UCMC, but multiple dialyzer use was routine at DCC. The starting point for entry to the study was, therefore, not the initial hemodialysis in patients with ESRD [9], but the first hemodialysis at DCC. All chronic HFH ESRD patients were entered into the study from their initial hemodialysis, since dialyzer reuse is practiced in HFH and satellite units. The period of limited care dialysis was deemed to begin at the time of the first hemodialysis at DCC or HFH satellite units and to end when one of the following occurred: (1) resumption of renal function so that dialysis was no longer required; (2) transfer to another limited care facility for hemodialysis treatment; (3) tramser to hemodialysis in the home; (4) transfer to treatment by intermittent or chronic ambulatory peritoneal dialysis (CAPD); (5) successful transplantation, so that hemodialysis was no longer required; (6) death occurring while the primary mode of tratment was hemodialysis, whether while the patient was being treated at DCC or had been transferred because of advanced illness to the UCMC inpatient or outpatient setting, and (7) the patient was alive, being treated by hemodialysis at the conclusion of the study on March 31, 1984 (DCC), or June 1, 1984 (HFH). Some patients were treated by hemodialysis, then had another form of treatment such as CAPD or transplantation, and later returned to treatment by hemodialysis. In these cases each period of hemodialysis was defined separately, and the total period the patient was at risk was summed.

Method of Hemodialysis

Single-pass, individual dialysate-delivery systems (Cobe Centry I & II and Seratrons) and hollow-fiber, capillary type dialyzers from several manufacturers were used. Details of the method of dialysis and of hepatitis B surveillance and prevention have been described [4]. The methods of dialyzer reuse adapted from *Hirsch* et al. [10] and *Levin* [11], the reasons for discarding of dialyzers, and the manner in which in vivo dialysance of dialyzers was tested have also been described [4]. On the average each dialyzer was used for six dialysis treatments. Formaldehyde was used as the sterilizing agent throughout. Formaldehyde levels in the air in the patient care area were monitored only recently; on two occasions the concentration was 0.09 and 0.09 ppm (DCC) and between 0.01 and 0.07 ppm (HFH).

Data Verification and analysis

Throughout the period of study, data on all DCC patients were entered routinely into an on-line computerized medical information system using a Digital Equipment VAX 11/780 computer; analysis was accomplished with the Digital Equipment Datatrieve query program [7, 8, 12]. At HFH patient data were entered retrospectively for the period 1972–1982 and routinely from 1982 to an on-line IBM 370/3081 system. Data were retrieved and analyzed using the Statistical Analysis System.

The number of patients at risk, the number of deaths, and certain other information were verified from independent sources: the records of the Ohio Valley (No. 17) and the Michigan (No. 14) ESRD Networks which maintain patient-specific registries of ESRD patients treated in these Networks. The data were compared with the Network patient registry data for all patients treated by dialysis at all facilities in Networks No. 17 and No. 14. The unadjusted dialysis mortality rate was also compared with national data from the ESRD registry, compiled from the semiannual surveys in all 32 ESRD Networks. These case fatality rates are calculated as the number of deaths in each year in patients who have received at least one treatment by dialysis (Hemodialysis and/or peritoneal dialysis) as outpatients or at home in each year. The number of patients treated is defined as the number on dialysis at the start of each calendar year plus the number starting outpatient dialysis for the first time during the year plus the number who restarted dialysis for any reason including those who returned to dialysis following cessation of function of a renal allograft.

Results

Excluding patients normally dialyzed elsewhere and treated only transiently, there were 259 DCC patients (117 males, 142 females; 119 Caucasians, 138 Negroes, 2 Orientals) and 1,059 HFH patients (615 males, 444 females; 497 Caucasians, 562 Negroes) who are the subject of this study. The age distribution was similar in the two groups. In all, 12.6% were <30 years, 14.9% were 30–39, 14.3% were 40–49, 24.1% were 50–59, 23.4% were 60–69, and 10.8% were 70 years or older. At DCC 78 patients (30.1%) had diabetes mellitus, 22 of whom were insulin dependent. At HFH, 251 patients (23.7%) had diabetes mellitus, 109 of whom were insulin dependent. In 13 of 56 DCC and 11 of 175 HFH patients with adult-onset diabetes mellitus ESRD was thought to have resulted from renal diseases other than diabetic nephropathy.

At the conclusion of the study the total duration of treatment by hemodialysis was as follows: in Cincinnati, 160 patients had been dialyzed in this setting for >1 year, 76 for >3, 24 for >5, and none for >7 years; in Detroit, the numbers were 362 patients for >1 year, 153 for >3, 116 for >5, and 43 for >7 years.

At the end of the period of observation, the number of patients who were still being treated and the average duration of hemodialysis treatment are shown in table 1. Also summarized are the reasons why treatment terminated before the close of the study. The 104 DCC and 235 HFH patients on hemodialysis at the end of the study had been treated for an average of 39.3 and 37.7 months, respectively.

Using the starting and ending points defined, the 259 DCC and 1,059 HFH patients were followed for totals of 535 and 2,209 patient years during which 72 and 396, respectively, died. Thus, the average survival on hemodi-

Table I. Patient status at the end of the study period and duration of treatment by hemodialysis in two facilities practicing the multiple use of dialyzers

Status of Patients	DCC			HFH		
	Patients		average treatment duration months	Patients		average treatment duration months
	n	%		n	%	
Treated by hemodialysis at the end of study	104	40.1	39.3	235	22.2	37.7
Received renal transplant	47	18.1	19.0	236	22.3	18.0
CAPD	17	6.6	14.1	38	3.6	28.2
Transferred to a dialysis unit elsewhere	15	5.8	12.3	122	11.5	18.2
Home hemodialysis	4	1.5	21.5	32	3.0	52.3
Died while being treated by hemodialysis	72	27.8	13.4	396	37.4	22.2
Total	259		24.8	1,059		25.4

Table II. Causes of death while being treated for ESRD by hemodialysis in two facilities practicing the multiple use of dialyzers

Cause of death	DCC	HFH
Proven or apparent myocardial infarction/arrhythmia	21	129
Infection/septicemia	11	86
Died at home, a cause unknown	11	39
Assumed hyperkalemia	7	27
Cerebral vascular accident	1	29
Withdrawal from dialysis	7	22
Cancer	6	20
Metabolic acidosis (? lactic acidosis)	1	9
Pulmonary emboli	2	7
Gastrointestinal bleeding	0	8
Systemic lupus erythematosus/scleroderma	1	5
Accidental	0	5
Anesthesia complications	1	4
Suicide	0	3
Ruptured aortic aneurysm	0	3
Dialysis dementia	2	0
Infarct of colon	1	0
Total	72	396

alysis was 7.43 and 5.57 years and the case fatality rate 13.46 and 17.92 deaths per treatment year, respectively. Most deaths (table II) were due to proven or presumed myocardial infarction, cardiac arrhythmia, hyperkalemia, or infection. Of 78 patients at DCC with diabetes mellitus 27 (34.6%) died, of 181 nondiabetics 45 (24.9%) died. Of 251 HFH patients with diabetes mellitus 118 (47.0%) died, of 808 nondiabetics 278 (34.4%) died.

One possible disadvantage of multiple dialyzer use is the association with an increased incidence of illness that requires admission to hospital (table III). Diabetic patients were admitted for an average of 2.66 (DCC) and 2.33 (HFH) times and for an average of 18.88 and 27.11 days per year, nondiabetics for an average of 1.30 (DCC) and 2.14 (HFH) times and for an average of 12.76 and 21.28 days, respectively, per year. Fifty-eight (DCC) and 104 (HFH) patients were never in hospital. Fifty DCC patients were in hospital <10 days. A high proportion of the total hospital stay was accounted for by a few patients: 18 DCC diabetics and 17 DCC nondiabetics were in hospital for a total of 51–100 days, 4 diabetics and 11 nondiabetics for 101–200 days, and 4 diabetics and 11 nondiabetics for >200 days. Of the diabetic HFH admissions 69% were for <10 days, as were 70% of the nondiabetic admissions. As at DCC, a few HFH patients accounted for a large proportion of admissions: 17% of diabetics for 46% of admissions of diabetics and 17% of the nondiabetics for 37% of admissions of nondiabetics. A positive test for hepatitis B surface antigen (HBsAg) developed in only 4 patients during 535 patient years at DCC and in no patient during 1,392 patient years at HFH.

Repeated exposure to formaldehyde has been considered a possible risk factor for cancer [13]. Data were available for all 535 DCC patient years and for the last 1,392 HFH patient years. In all, there were 62 malignant tumors in 1,009 patients; 33 developed before ESRD. In 9 patients multiple myeloma was the cause of renal failure; 4 are alive after an average of 3.75 years on dialysis, and 1 was transferred elsewhere. In 2, hypernephroma and bilateral nephrectomy resulted in renal failure; 1 was

Table III. Number of admissions and days of hospitalizations for patients treated by hemodialysis in two facilities practicing the multiple use of dialyzers[1]

	Diabetics		Nondiabetics		Total	
	DCC	HFH	DCC	HFH	DCC	HFH
Number of patients	78	76	181	285	259	361
Total years of follow-up	130.8	77.0	403.3	237.9	534.0	314.9
Number of admissions[2]	348	179	523	509	871	688
Number of days in hospital[2]	2,468	2,088	5,147	5,061	7,615	7,149
Admissions per year	2.66	2.33	1.30	2.14	1.63	2.19
Days in hospital per year	18.88	27.11	12.76	21.28	14.26	22.71

[1] Data for DCC are for the entire period of study from July 1977 to March 1984. For HFH the admissions and days in the hospital are for the last 18-month period from January 1983 to June 1984.

[2] Includes admissions for all causes except transplantation and planned catheter placement for CAPD.

transferred elsewhere, the other has been treated by dialysis for 4 years without evidence of metastases. In 5 cases metastatic disease occurred during dialysis treatment from tumors present prior to dialysis. Of 4 with breast carcinoma prior to starting dialysis 1 developed metastases and died 8 years after starting dialysis; the other 3 have no evidence of metastases. Twenty-eight tumors, including the new metastases, have developed since hemodialysis treatment started, i.e., 1 new tumor per 68.78 patient years on dialysis. At DCC 6 of the 12 new tumors (3 in the colon and 1 each in the skin, thyroid, and gall bladder) were detected early.

Special consideration is given to patients who were treated by hemodialysis for > 5 years. Of the 140 patients dialyzed in Cincinnati and Detroit for > 5 years 36 (average age 61 years) had died, and 104 (average age 55.4 years) were alive at the end of the study. Of the living patients all but 7 cared fully for themselves. Nineteen had diabetes mellitus. Twelve patients had had a myocardial infarct prior to starting dialysis; since starting dialysis 25 had angina pectoris, 21 a myocardial infarct. Five patients developed cerebral hemorrhage or thrombosis. Twelve had amputations of the lower extremity, and 26 had had a parathyroidectomy.

Discussion

Results of treatment in any disease depend on many factors; without a multifactorial analysis, it is difficult to assess the role of any single factor. In this study the focus of concern is on survival and morbidity in two separate groups of patients treated by chronic maintenance hemodialysis with dialyzers that are used on multiple occasions. As all patients were treated by the mode of therapy reported, it is impossible to evaluate its precise role in the outcomes reported. Our purpose is to evaluate whether there is any discernible adverse effect consequent on long-term use of dialyzers that are used on multiple occasions. We, therefore, limit the discussion to the outcomes in these patients, compared whenever possible to outcomes in patients treated elsewhere.

Favero et al. [14] reported that the practice of reusing dialyzers was not associated with an increased risk of hepatitis B infection among patients and staff, an observation confirmed herein. In patients treated by hemodialysis in the United States the incidence of HBsAg was 3.0, 1.0, and 0.5% in 1976, 1980, and 1982, respectively [15, 16]. The incidence of HBsAg conversion was 0.7% per year for patients at DCC and 0 for patients at HFH. In the United States the prevalence at the end of each of 1976, 1980 and 1982 in between 33,000 and 66,000 patients was 7.8, 3.8, and 2.7%, respectively [15, 16]. Over the 7 years of study (December 1977 to December 1983 inclusive) the cumulative prevalence was significantly less at both DCC and HFH.

Another possible concern is the occurrence of anti-N antibody and its relation to dialyzer reuse [17, 18]. When a point prevalence study was done on the Cincinnati patients, only 5.9% of the 68 sera examined were positive, a prevalence not higher than that reported by others.

The rate of hospital admission and duration of hospital stay reported herein are similar to those reported in an earlier analysis from DCC [4]. They are slightly lower than that reported by *Avram* [19] whose diabetic and nondiabetic patients were admitted to hospital on the

Table IV. Case fatality rate in all patients treated by chronic maintenance hemodialysis and peritoneal dialysis in the years 1980–1983 and who received one or more dialysis treatments as outpatients

Source	Year	Patients at risk	Deaths	Fatality rate
United States	1983	92,250	14,020	0.152
	1982	83,854	12,502	0.149
	1981	75,557	11,401	0.151
	1980	67,729	10,213	0.151
	1980–1983	319,390	48,136	0.151
Network No. 17	1983	1,943	319	0.164
	1982	1,792	271	0.151
	1981	1,563	242	0.155
	1980	1,380	>253	>0.183
	1980–1983	6,678	1,085	0.162
UCMC-DCC	1983	196	22	0.112
	1982	195	23	0.118
	1981	171	19	0.111
	1980	162	18	0.111
	1980–1983	724	82	0.113
Network No. 14	1983	3,174	528	0.166
	1982	3,042	493	0.162
	1981	2,693	422	0.157
	1980	2,384	393	0.165
	1980–1983	11,293	1,836	0.163
HFH	1983	393	70	0.178
	1982	354	48	0.135
	1981	328	52	0.158
	1980	338	53	0.156
	1980–1983	1,413	223	0.157

Sources: United States data from ESRD Medical Information System, Health Care Financing Administration, and Network data from Ohio Valley and Michigan Renal Disease Network Patient Registries.

Mean age of patients: in Network No. 17 51 years; in Network No. 14 50 years; in DCC-UCMC 49 years; in HFH 50 years.

Patients with ESRD due to diabetic nephropathy: Network No. 17 17.8%; Network No. 14 19.2%; UCMC-DCC 25.1%; HFH 23.7%.

Patients with any form of health insurance at start of ESRD treatment: Networks No. 17 and No. 14 unknown (?75–80%); UCMC-DCC 50%; HFH 62%.

average 2.4 and 1.84 times per year, respectively. The number of days in hospital for our nondiabetic patients was 12.8 (DCC) and 21.3 (HFH) per year; this is similar to the 15.7 days reported by *Shapiro* and *Umen* [20]. Our diabetics were in hospital for an average of 18.9 (DCC) and 27.1 (HFH) days per year; this is similar to or lower than the rates reported recently by *Shapiro* and *Umen* [20], *Shapiro* [21], and *Legrain* et al. [22]. For the whole group of patients the rate of hospitalization is lower than or similar to the 19.29 days per year reported for patients treated by hemodialysis at the Northwest Kidney Center [23] and the 16.3–23.2 days per year for patients treated by CAPD [24–26]. It is virtually identical to that reported recently by ESRD Network No. 7 [27].

To compare the mortality rate in our patients with that reported by others we have used the data base for the number of deaths and the number of patients dialyzed that is used in other reports. Included, therefore, in this comparison are all who received one or more hemodialysis or peritoneal dialysis treatments as outpatients, whether in the limited care or hospital outpatient setting. Thus, the sicker patients who are more likely to die early and before reaching the level of stability that ensured their transfer to DCC and HFH satellite units are included.

Using these criteria the unadjusted dialysis mortality rate of the patients treated at DCC-UCMC in the 4 years 1980–1983 inclusive was 11.3% (table IV). The UCMC-DCC study group included 10 patients who received 17 calendar years of care and were treated as outpatients by peritoneal dialysis only; 7 died. If they are excluded, the case fatality rate for patients who received one or more hemodialysis treatments as outpatients in any calendar year was 10.6%. It is lower than the 14.2% reported by *Avram* [19] in 1979. At HFH the number of patients treated by peritoneal dialysis was so small that it did not impact significantly the mortality rate with these cases excluded. The results are compared with National and with Ohio Valley (No. 17) and Michigan (No. 14) ESRD Network data (table IV). The national unadjusted dialysis case fatality rate for all patients treated by all modes of dialysis during 1980–1983 was 15.1% [28]. In the same years the case fatality rate in Network No. 17, computed on data from the Network patient registry, was 16.2% [29] – 16.8% when UCMC-DCC patients are excluded. In Network No. 14, when HFH patients were excluded, the case fatality rate of 16.3% was unchanged. Thus, the case fatality rate was significantly less ($\chi^2_{(1)} = 14.45$; $p < 0.0002$) in the UCMC-DCC facility and equal to the Network in the HFH facilities in which the hemodialyzers are used routinely on multiple occasions. These results do not appear to be due to selection; in both present series there was a higher proportion of patients with each of two major risk factors: (1) diabetic nephropathy and (2) no form of health insurance [8] when treatment by dialysis commenced.

These observations are consistent with the view that treatment by hemodialysis making use of the dialyzer on many occasions was not associated with an increase in morbidity or mortality. The results are from two programs in which special attention has been paid to the quality of methods used for reprocessing dialyzers. It seems reasonable to suppose that equally good outcomes may be expected in those programs in which equally strict standards are the routine practice.

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Mortality and morbidity of reusing dialysers

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A report by the registration committee of the European Dialysis and Transplant Association

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Summary and conclusions

The practice of reusing dialysers in renal units in the UK was surveyed by examining the patient questionnaires returned to the EDTA registration committee for 1976 and by a special questionnaire sent to all UK renal units. Altogether 65·6% of the 1785 patients treated with non-disposable dialysers and 40·6% of the 1100 treated with disposable dialysers reused their equipment. Reuse of dialysers caused some morbidity but no mortality.

Most centres where disposable dialysers were used accepted that their reuse was necessary because of financial constraints and was ethically defensible.

Introduction

Although effective in preventing death due to end-stage renal disease,[1] regular haemodialysis is expensive. The cost of treatment in the United Kingdom was recently estimated to be £10 000 per year per patient for hospital haemodialysis and £6000 per year for home haemodialysis.[2] Most doctors therefore accept that they should make all possible economies in materials and staff. Economic measures may reduce safety and additional risks must be acceptable both medically and legally.

Disposable dialysers are gradually displacing non-disposable ones in the UK because they have several advantages over the non-disposable (Kiil) type. They are easier to store and use and patients can use them at home without the structural alterations that may be necessary to accommodate a Kiil dialyser.

Disposable dialysers do not, however, provide dialysis as cheaply as non-disposable parallel-flow dialysers. A modern Meltec Multipoint dialyser with trolley costs £560, and yearly costs for membranes, blood ports, and regasketing are about £100. The dialyser boards and trolley will probably serve an individual patient for at least two and possibly three or four years. The average annual cost for this equipment is thus £240 to £380. Disposable dialysers cost from £10 to £25 each, depending on the type and on bulk purchasing agreements. They therefore cost six to 14 times as much per year as non-disposable equipment. The cost can be reduced if the haemodialysers are not discarded after use but rinsed and resterilised for reuse. If they are reused three times disposable dialysers are only about twice as expensive as non-disposable equipment, and after seven reuses they are beginning to be cheaper. (These cost comparisons are based on material costs alone. The building, testing, and sterilising of the Kiil type of dialyser takes about one man-hour and unless the patient carries this out himself a skilled kidney builder must be paid to do it.)

We surveyed the practice of reuse in renal units in the United Kingdom and investigated its mortality and morbidity. We also inquired about the views held in renal units about the necessity and ethics of reusing "disposable" dialysers.

Methods

The registration committee of the European Dialysis and Transplant Association collects yearly returns from all UK centres as part of a survey covering 27 countries.[3] Information is returned on individual patient questionnaires, which record (among other data) the type of dialyser used most often for the patient and the average number of reuses of the dialyser. Returns for 1976 were received from 54 out of 56 UK units.

Mortality in patients who reused disposable dialysers was compared with mortality in patients who did not reuse. To remove bias due to

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disparities in the age distribution in the two groups we studied only patients aged 15-34 years.

Morbidity was assessed by a special questionnaire circulated among UK units which included questions on pyrexial reactions, bacteraemias, other types of cross infection, and incidents associated with sterilising agents.[4] We also asked about any other complications attributed to reuse, including membrane rupture.

Opinions about reusing dialysers were sought by presenting a spectrum of views from which respondents could select those with which they agreed. Replies to this special questionnaire were received from 49 out of 56 units. Thirty-three units had some experience of reuse of disposable dialysers; 16 did not reuse.

Results

Information on the types of dialysers and on the practice of reuse in the United Kingdom is given in tables I and II. Comparison with previous years' analyses indicates that the proportion of patients using disposable dialysers is increasing while the proportion using non-disposable dialysers is decreasing. In this trend the United Kingdom has followed European practice, but over 60% of UK patients still used non-disposable parallel flow dialysers in 1976 compared with 11% of European patients.

TABLE I—*Percentage of patients using different groups of dialysers, Europe and UK 1973-6*

Year	Non-disposable parallel flow	Disposable			Total No of patients
		Parallel flow	Coil	Hollow fibre	
			Europe		
1973	23·9	28·7	38·2	6·5	16 332
1974	20·4	33·5	37·9	7·5	22 233
1975	13·7	40·3	35·4	10·6	25 971
1976	11·0	42·2	35·8	10·4	30 522
			UK		
1973	73·7	9·0	10·6	3·8	2 054
1974	68·1	7·0	17·5	6·6	2 304
1975	66·1	8·9	13·3	10·3	2 648
1976	61·6	13·5	13·4	11·6	2 894

TABLE II—*Number of patients using and reusing different groups of dialysers UK 1976. (Total number of uses per patient among those reusing dialysers is equal to number of reuses plus one.)*

	Non-disposable parallel flow (plate)	Disposable		
		Parallel flow (plate)	Coil	Capillary (hollow fibre)
		Hospital haemodialysis		
No of patients ..	517	188	206	179
No of patients who reused	195	75	20	85
Average reuses per patient who reused	3·0	4·2	5·4	3·8
		Home haemodialysis		
No of patients ..	1268	197	183	156
No of patients who reused	976	157	80	113
Average reuses per patient who reused	3·2	3·0	5·6	1·8

The proportion of patients undergoing hospital dialysis was smaller than that of home dialysis patients, and this remained true when the groups of dialysers were considered separately. Those hospital patients who did reuse dialysers, however, got an average of over six uses from coil dialysers and about five uses from the disposable parallel flow and capillary dialysers; patients undergoing dialysis at home achieved fewer reuses, except in the groups reusing disposable coil dialysers and non-disposable parallel flow dialysers.

Mortality after the first 12 months' treatment in the patients who regularly reused disposable dialysers was lower in both home and hospital groups than in those who did not reuse (table III). A joint analysis of results in five European countries where a high proportion of patients regularly reused disposable dialysers confirmed this result. A special question inserted into the centre questionnaire established that no deaths occurred in the United Kingdom that were thought to have been avoidable if reuse had not been practised.

TABLE III—*Mortality in patients (aged 15-34) reusing and not reusing disposable dialysers, UK and five European countries combined 1976*

Practice	Hospital dialysis		Home dialysis	
	No of patients	% Mortality at 1 year	No of patients	% Mortality at 1 year
		UK		
Reusing	98	6·5	61	0
Not reusing	130	15·6	66	12·5
		France, West Germany, Italy, Switzerland, UK		
Reusing	591	6·9	192	6·0
Not reusing	3491	8·8	335	5·1

Of the 33 units in which disposable dialysers had been reused, 13 reported pyrexial reactions and three bacteraemia due to reuse. Several units pointed out that febrile reactions may occur on first use of a disposable dialyser and some thought that they occurred even more often with non-disposable dialysers both on first use and with reuse. Many units had studied methods for rinsing and sterilising, and one claimed that all problems due to non-bacterial reactions had now been "totally eliminated." No cases of cross infection with hepatitis B antigen were recorded. Nine units reported incidents associated with sterilising agents when reusing equipment, and two units specifically mentioned the development of anti-N antibodies. Nine units experienced mechanical problems, particularly membrane rupture and occlusion of fibres in hollow-fibre dialysers. Several units were concerned to establish that the decrements in clearances and increases in residual blood volume were acceptable. Some suggested that results were not always reproducible and that successful reuse depended to some extent on the individual patient and perhaps on his heparin regimen during dialysis.

Attitudes on reuse varied widely. Seven units thought that the practice was "potentially very dangerous," and one stated categorically that all patients should be treated with disposable dialysers used only once. Nevertheless, 27 of the centres practising reuse thought that the morbidity and inconvenience were negligible and that reuse was "inevitable in the present economic climate." Twenty-one centres agreed that the morbidity could be almost completely eliminated by good technique, and nine thought that when mishaps occurred these were always the fault of the staff preparing the dialyser. Thirteen centres were irritated by the time taken to carry out the procedure and two had refused to adopt it because of inadequate staffing. Eight centres got round these practical objections by delegating the task to the patients themselves, and four centres used either specially adapted proportionating equipment or separate automated equipment to perform the task.

Discussion

Our assessment of the mortality and morbidity caused by reusing disposable dialysers indicates that reuse carries appreciable morbidity but no detectable mortality. With some notable exceptions, most UK renal units are prepared to consider it a reasonable compromise: it is accepted as a necessary cost to ask of patients so that more patients may be treated and also enjoy the advantages of the compact and convenient disposable dialysers. As some of our respondents pointed out, if the morbidity of reuse was considered unacceptable they would be forced back to the cumbersome Kiil type of dialyser and the procedure for preparing this is almost the same as the procedure for preparing a disposable dialyser for reuse.

It would seem more relevant to explore techniques for reuse and to assess the various competing disposable dialysers to see how many uses can be obtained from each of them without a decline in efficiency or frequent mechanical problems. Some studies have already been published on the reuse of certain disposable dialysers.[5 6] Further information is needed to assess how dialyser design, rinsing techniques, and the patient himself affect the success of repeated reuse.

There is understandable commercial resistance to the reuse of disposable dialysers. Because manufacturers do not authorise the practice officially some centres that have wanted to reuse and save money with which to treat other patients have been stopped from doing so by their hospital administration because of fears of litigation. This embargo might also gain support from bacteriological purists. Were it to become nationwide, however, it would result in extra expenditure of almost £1m a year solely to eliminate the reuse of disposable dialysers on the scale practised in 1976. This money could fund 150 patient-years' home dialysis at the costs quoted in our introduction.

Financial constraint has made it necessary for many physicians to decide to reuse "disposable" dialysers. Ethical responsibility for this decision must remain with the clinician. Nevertheless, the results of our survey should show that there is no need to fear any inquiry by the courts.

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Exclusive Presentation of Important NKF Consensus Reuse Standards

NATIONAL KIDNEY FOUNDATION REVISED STANDARDS FOR REUSE OF HEMODIALYZERS

December 2, 1983

The Executive Committee of the National Kidney Foundation has decided to issue these Standards for Reuse of Hemodialyzers in the interest of better patient care.* These standards will be reviewed periodically as the science of dialyzer reuse develops. Accordingly, the Foundation requests comments and suggestions from all interested parties.

The practice of reuse of hemodialyzers, which involved 18 percent of U.S. patients in 1978, increased to 27.5 percent of U.S. patients in the fall of 1981. Recent CDC surveillance of 1,015 dialysis facilities [out of about 1,300 total] treating 65,812 patients showed that, as of December 31, 1982, 43 percent of facilities and 51 percent of patients were utilizing dialyzer reuse. It is appreciated that new dialyzers contain potentially toxic residues of the manufacturing process, and that used dialyzers contain potentially toxic residues of the reprocessing procedure. It is also recognized that appropriate procedures are capable of reducing the levels of these residues to the point that acute reactions to new and to used dialyzers are infrequent, and that chronic toxicity has not been described. It is important, however, to continue long-term studies of potential toxicity of new and used dialyzers.

Manufacturers of new dialyzers appropriately utilize a number of different techniques to produce dialyzers, but all new dialyzers must meet certain standards of safety, usually assumed by validation studies of a small sample of the product. Each dialyzer type is credited with certain standards of performance based upon manufacturing specifications and supported by periodic validation studies of small samples of the product. Similarly, a facility that reprocesses dialyzers is responsible for producing a safe and effective product (FDA Compliance Policy Guide 7124, 23, Nov 1977). Although a number of different techniques are appropriately utilized to reprocess dialyzers, the growing practice of dialyzer reuse now makes it mandatory to develop standards of safety and performance for reprocessed dialyzers.

The patient has the right to expect—and the facility the obligation to provide—professional, safe and effective care at all times. A system, and specific written procedures, concerning all elements of dialyzer reuse should be developed by each facility practicing reuse. These aspects of reuse are appropriately individualized to the particular facility, but should be directed to achieve an effective, safe system, and a uniform product.

The system should provide suitable discrete space for reprocessing and storing used dialyzers; define and document personnel training; assure personnel safety by written protocols and training concerning safe handling of toxic substances; provide procedures for spills and splashes of toxic substances; provide devices for protection from toxic substances (goggles and masks); and provide for control and monitoring of toxic fumes to or below recognized Occupational Safety and Health Administration (OSHA) standards.**

> ***If formaldehyde is used as the disinfecting agent, a minimum concentration of four percent in both the blood and dialysate compartments, and a minimum exposure time of 24 hours is mandatory. This standard is developed in keeping with recent CDC studies.***

The product must meet minimum standards which should include individualization of dialyzers, safety in subsequent application, effectiveness during subsequent use, a suitably esthetic product, and consent.

INDIVIDUALIZATION

1. Each dialyzer to be reused must be indelibly and clearly labeled with the patient's name and other unique identifying information before or during the initial use.
2. At each subsequent use, the label should be checked by two separate individuals, usually the dialysis staff member and the patient, if feasible.
3. The number of the use should be recorded both in a reuse record maintained for each dialyzer, and in the patient's permanent dialysis record.

This standard should assure individualization of the dialyzer, permit retroactive tracking of the dialyzer in the event of dialyzer failure or reaction during use, and generate records of performance of reprocessed dialyzers suitable for program analysis.

In addition, reuse of dialyzers is not recommended in patients who are Hepatitis B antigen positive because of the potential risk of transmission of hepatitis to dialysis staff and other patients.

SAFETY

Safety of the reprocessed dialyzer is assured by the use of suitable solutions for rinsing, cleaning and disinfecting the dialyzer, and by the subsequent effective removal of these solutions.

1. Water used to formulate cleaning solution and to rinse dialyzers shall be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter (0.45 micron) which is appropriately maintained. This water must contain less than 200 bacteria per mL, which should be documented by bacteriologic sampling of the source water outlet in the reprocessing area at least monthly. Where such sampling reveals bacterial counts that periodically approach or exceed this limit, corrective measures and weekly sampling are indicated. Results of such samples should be appropriately recorded.
2. Water containing a level of bacterial endotoxin (pyrogen) of less than 1 mg/mL, documented by a suitably sensitive, negative limulus amoebocyte lysate (LAL) test not less than monthly, must be used to formulate the disin-

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fecting solution. A sub-micronfilter, in line between the disinfectant reservoir and the disinfectant outlet is necessary to remove particulates.

3. There is little information concerning the effect of chemicals commonly found in potable water on any aspect of reprocessing, its effectiveness, or its safety. Therefore, no standard is proposed. However, the possibility of chemical absorption by the dialyzer membrane during reprocessing and unknown effects of such absorption on safety and efficacy of reuse suggest the need for further study of this question and have prompted some facilities to use water meeting AAMI chemical standards in reprocessing dialyzers.

Recent U.S. Centers for Disease Control surveillance of 1,015 dialysis facilities (out of about 1,300 total) treating 65,812 patients showed that, as of December 31, 1982, 43 percent of facilities and 51 percent of patients were utilizing dialyzer reuse.

4. Disinfection must be achieved with an effective agent, the addition of which to each dialyzer must be documented and recorded. If formaldehyde is used as the disinfecting agent, a minimum concentration of four percent in both the blood and dialysate compartments, and a minimum exposure time of 24 hours is mandatory. This standard is developed in keeping with recent CDC studies. Further investigation is required to determine if lower concentrations of formaldehyde effectively eliminate fastidious organisms found in some water sources. If any other disinfecting agent is employed, effective concentrations, contact characteristics, and exposure time must be established and utilized and shown to be equivalent to formaldehyde in effectiveness.
5. Disinfection should be monitored epidemiologically by means of a log of all febrile reactions during dialysis with new or used dialyzers, and a written procedure including dialysate and blood cultures during all febrile reactions. A febrile reaction rate greater with used than with new dialyzers requires a careful reevaluation of all elements of the disinfection process. Routine validation studies of blood compartment disinfection are not productive in the clinical setting.
6. Documentation and recording of the addition of effective disinfectant concentrations in the dialyzer to be reused is mandatory.
7. Documentation and recording of effective disinfectant removal from each dialyzer immediately prior to reapplication is mandatory. If formaldehyde is used as the disinfecting agent, a Schiff's reagent-based test, negative after five minutes, is suitable screening test for each dialyzer. Validation tests of methodologic achievement of 5 mcg/mL (5 ppm) or less should be made at least monthly.
8. Removal of any other potentially toxic substances added as any part of the reprocessing procedure should also be documented and recorded by routine testing and/or validation studies as may be appropriate.

EFFECTIVENESS

1. The effectiveness of the reprocessing procedure must be documented before each subsequent use of each dialyzer.
2. For hollow fiber dialyzers, a hollow fiber bundle volume (HFBV) of not less than 80 percent of the initial HFBV, measured at 0 ± 10 mm of Hg transmembrane pressure, is a sufficient measure of residual effective function.
3. At the present time, no satisfactory, generally acceptable test exists to measure residual function of parallel plate or coil dialyzers except small molecular clearance, which precludes multiple use of plate and coil dialyzers at this time, unless clearance tests are performed after or during each use.
4. Blood leaks during use of both new and reprocessed dialyzers should be documented and recorded. If the blood-leak rate of used dialyzers exceeds that of new dialyzers, each dialyzer must be pressure tested for possible blood compartment leak before reuse.
5. Validation studies including at least *in vivo* or *in vitro* clearances of creatinine and urea and ultrafiltration rate of each dialyzer type reprocessed by a facility should be conducted not less than quarterly.

ESTHETIC APPEARANCE

A critical visual inspection of each dialyzer is necessary to detect cracked or broken parts, and to assure a clean, pleasing appearance. It is unreasonable and inappropriate to present an esthetically unattractive dialyzer to the staff or patient for reuse.

1. Reprocessed dialyzers must appear clear, and free of dissolved or residual blood manifest by a brownish or pinkish tinge.
2. A few (five or less) visible, dark, clotted fibers are acceptable.
3. The headers should be visibly free of all but small peripheral clots.
4. Failure to meet these criteria requires that the dialyzer be discarded.

CONSENT

Ethical aspects of dialyzer reuse concern the rights of the several members of the dialysis community. All members of the community benefit from Medicare funding for End-Stage [redacted] Disease care, and all share the [redacted] for limiting program costs, while [redacted] access to quality care. The principles of informed consent are a truthful presentation of possible complications and hazards of therapy, the benefits to be expected from therapy, and the alternatives to hemodialysis therapy.

Patient informed consent for the reuse procedure as practiced by the center at which the patient dialyzes is essential. If patients do not sign a consent form to reuse, they are entitled to a new dialyzer for each hemodialysis treatment.

MISCELLANEOUS

Reuse of dialyzers by individual home patients has been safely and effectively practiced for many years. This practice should observe the same principles, and the same specific standards, elaborated for reuse in facilities. A system for reprocessing should be established and monitored by the home training facility with written procedures and training directed toward the protection of the patient and family members from injury in handling and using toxic substances. Procedures, training, and testing should be provided to assure the safety and effectiveness of reprocessed dialyzers, the same as for dialyzers reprocessed by the facility. All procedures should be reviewed semi-annually in the home setting for compliance.

These standards are intended to assure safe and effective multiple dialyzer use, but are not intended either to encourage or constrain this practice. A specific limit on the number of uses of any reprocessed dialyzer is arbitrary and inappropriate, as long as all the criteria of individuality, safety, effectiveness and appearance are met. The standards are readily achievable, represent currently available and practiced technology, and should be periodically modified by the consensus of broadly representative and expert assemblage as technology changes. ☐

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*The National Kidney Foundation convened a group with expertise and experience in dialysis, including one or more physicians, nurses, consumers (patients), industry representatives, and microbiologists to formulate these standards, which were subsequently approved by the Executive Committee of the National Kidney Foundation at its December 2, 1983 meeting.

**The standard for formaldehyde requires an 8-hour time weighted average (TWA) concentration limit of 3 ppm, a ceiling concentration of 5 ppm, and an acceptable maximum peak above the ceiling concentration of 10 ppm for no more than a total of 30 minutes during an 8-hour shift.

(NOTE: THIS DOCUMENT WAS INCLUDED IN THIS RECORD AT THE REQUEST OF SENATOR JOHN GLENN, RANKING MINORITY MEMBER OF THE SPECIAL COMMITTEE ON AGING.)

DIALYZER MEMBRANES: SYNDROMES ASSOCIATED WITH FIRST USE, AND EFFECTS OF MULTIPLE USE

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ABSTRACT

Symptoms occurring with the first and subsequent use of dialyzers were analyzed in studies from a single limited care dialysis unit. More symptoms occurred with the first use of the dialyzer. The rate of their occurrence during the first use appeared to be related to membrane type, method of dialyzer preprocessing, and individual patient characteristics. A severe syndrome associated with the first use of dialyzers has been reported on 4-8 occasions per 100,000 dialyses, and to be associated particularly with cuprammonium cellulose hollow fiber dialyzers. Our data confirmed this, and suggested that the syndrome might be prevented by effective preprocessing of new dialyzers.

Many dialyzers of different membranes, design, and manufacture, are currently in use. To assess the effectiveness of and complications associated with any individual membrane, and to compare the data with those using other membranes is a demanding task requiring a comprehensive data base. Unfortunately, few such comprehensive data bases exist.

At Dialysis Clinic-Cincinnati, a computerized medical information system has been in use in hemodialysis since 1977 (1,2). Using this data base it was shown that the practice of reusing dialyzers was safe (3), and that this practice did not affect patient survival adversely (4).

Symptoms Occuring with New and Reused Dialyzers

The occurrence of more symptoms associated with the first than with the subsequent use of the dialyzer has been suggested (5) and shown in a prospective study of 948 dialyses in 29 patients (6). In 1985, Robson and his colleagues (7) reported observations on 26,592 dialyses using 4933 new dialyzers, which had been processed manually by the method outlined in Table 1 prior to both the first and subsequent uses. Symptoms in general occurred 1.3 times more frequently with the first than with the subsequent use of the dialyzer; for each individual symptom the incidence during subsequent use was similar to or less frequent than that during the first use of the dialyzer (Table 2). Certain symptoms including hypotension, cramps, nausea/vomiting, headache, itching, chest pain, back pain, shortness of breath, chills, and tremor--were significantly more frequent during the first use.

A Mild First Use Syndrome of Concurrent Chest and Back Pain

Two relatively infrequent symptoms, chest pain and back pain, occurred respectively 2.8 and 6 times more frequently with the first use (Table 3). These two symptoms, chest pain and back pain occurred concurrently 42 times more frequently during first use, and appeared to constitute a first use syndrome (7). This syndrome occurred with 41/2589 (1.58%) dialyzers made of regenerated cellulose, with 6/826 (0.75%) made of saponified cellulose ester, and with 9/1446 (0.62%) made of cuprophan. The total number of complications per dialysis was 1.0, 1.13, and 1.01 with dialyzers made respectively of regenerated cellulose, saponified cellulose ester, and cuprophan (7).

These findings suggest that the type of membrane used may influence the incidence of this first use syndrome. Other factors also appear to be involved. Although there were 147 patients in this study, this first use syndrome occurred 57 times in only 24 individual patients. In 15 it was observed once; in 2 patients each, it was observed on 2, on 3 and on 5 occasions; and in the other 3 it was observed on 4, on 7 and on 11 occasions. In the patient with 11 episodes of concurrent chest and back pain, 6 were with cuprophan, 3 with saponified cellulose ester, and 2 with regenerated cellulose dialyzers. Characteristics individual to the patient may also be important in determining whether this syndrome occurs.

Effect of Method of Dialyzer Preprocessing and Reprocessing

In 1984 the method of processing dialyzers was changed from a manual to a machine method detailed in Table 1. The incidence of symptoms occuring during 12,395 successive dialyses, using 1037 new dialyzers processed by the machine method, was then analyzed (8). Symptoms in general occurred 1.13 times more frequently with the first use of the dialyzer, and the incidence of most individual symptoms differed little during the course of the first and subsequent use (Table 2). After the machine method of processing new dialyzers was instituted, the incidence of chest pain and back pain decreased strikingly during the first use of the dialyzer (Table 3), and was similar during the first and subsequent use of the dialyzer. The previously observed first use syndrome, i.e. the simultaneous occurrence of chest and back pain, occurred only once with 1037 new dialyzers. These observations suggest that the manner in which the dialyzer is processed prior to its first use is an important variable.

The Severe First Use Syndrome

Attention has been focused recently on a more severe syndrome associated with the first use of the dialyzer. Described in detail by Daugairdas and his colleague (9), this reaction appeared typically within minutes of initiation of dialysis and was characterized by cardiopulmonary, mucocutaneous, and/or gastrointestinal tract symptoms suggestive of anaphylaxis. These authors described 21 such severe reactions in about 260,000 hemodialyses (8.1/100,000 dialyses) at three centers in Chicago over a 10.5 year period. There were 4 respiratory arrests, and one death. A survey conducted in 1982 to 1984 by a cooperative effort among the Health Industries Manufacturers Association, seven dialyzer manufacturers, and the United States Food and Drug Administration (9) found that, with hollow fiber dialyzers, 362 such reactions occurred with over 8.4 million dialyzers, a reaction rate of 4.3 per 100,000 dialyzers. There were only 4 reactions with 2.1 million flat plate dialyzers, a rate of 0.2 per 100,000. No reactions were reported with 639,000 coil dialyzers; this number is too small to be certain that the absence of reactions is significant. Death resulted in 2.8% of the reported reactions, a death rate of 0.12/100,000 dialyzers, and 0.09/patient year/1000 patients. Clearly, to explain such infrequent reactions satisfactorily is extremely difficult. This study (9) suggests that there are important host effects, for reactions occurred 3.2 times more frequently in subjects <30 years of age than in those >50, and the incidence was 2.8 times higher in blacks than in whites.

Details of the Chicago study are important (Table 4). There were no such reactions with almost 70,000 dialyzers made of regenerated cellulose, with over 50,000 of cellulose acetate, and with over 2,000 of saponified cellulose ester. With hollow fiber dialyzers made of cuprophan, however, the reaction rate was 56.7 per 100,000. Plate dialyzers made of cuprophan were also responsible for reactions, but at a lower rate of approximately 4 per 100,000. Over 46,000 coil dialyzers and 2,788 plate dialyzers of polyacrylonitrile were used without reaction. These observations suggest that hollow fiber dialyzers made of cuprophan are particularly liable to be associated with reactions. That it is not cuprophan per se is suggested by the lower rate of reactions with cuprophan plate dialyzers. No data are available on a large series of hollow fiber dialyzers made of polyacrylonitrile and the number of plate dialyzers used and reported in the Chicago study is too small for assurance that this severe syndrome does not occur with this membrane.

It seemed appropriate to inquire whether observations made on the milder syndrome of concurrent chest and back pain might cast light on the more severe anaphylactic type of reaction. The known characteristics of the two patient populations are summarized in Table 5; they are clearly different. It appeared that the mild first use syndrome was related not only to the use of cuprophan hollow fiber dialyzers, but also to the way in which they were processed before use. In the Chicago study 33,510 cuprophan hollow fiber dialyzers were used and 19 reactions occurred, a rate of 56.7 per 100,000 dialyses. Cuprophan hollow fiber dialyzers have been used at Dialysis Clinics, Cincinnati since 1979. We have not been able to completely analyze all dialyses done with these dialyzers.

Complete stock records indicate that a total of about 4,200 such dialyzers were used. Each was used about 10 times. Thus about 42,000 hemodialyses were done with cuproammonium cellulose dialyzers. There was a single very severe reaction and 2 milder reactions, a rate about 12% of that expected (Table 6). As in the Chicago study these 3 reactions all occurred within a short period of time; each was with a cuproammonium cellulose dialyzer to which the patient had not been exposed previously.

We examined the experience with cuproammonium dialyzers in the light of the method of processing of the dialyzer (Table 6). Assuming 10 uses per dialyzer there were 37,800 exposures to a dialyzer that had been reprocessed manually or by machine, and no severe reactions; there were about 4,200 exposures to a new dialyzer and 3 reactions (71.4/100,000). From October 1981 onwards all dialyzers used at Dialysis Clinic had been preprocessed either by the manual or by the machine method prior to a first use on the patient. Of 4,200 new cuproammonium dialyzers, approximately 3,700 were preprocessed before the initial use; there were no severe reactions. Only about 500 dialyzers, at most, were received "dry pack" and processed only by saline rinsing prior to the first use; all 3 severe reactions occurred in this group. This is a rate of 600 per 100,000 dialyzers.

These observations strongly suggest that there are as yet unrecognized factors present in new dialyzers, and that they are eliminated by effective preprocessing of the dialyzer before its first use. This view is strongly reinforced by the circumstances of the only death of which we are aware in one of our patients, a 49-year-old black female. She developed an acute reaction, respiratory arrest, became decerebrate, and died. The respiratory arrest occurred within the first 15 minutes of the first use of a new type of cuproammonium dialyzer that had been processed with saline. This patient had received 321 dialyses under our care, 312 of which were with preprocessed cuproammonium dialyzers. At no time had she had any reaction. The severe fatal reaction occurred on vacation, when dialyzed for the first time in another dialysis unit and exposed for the first time to a saline rinsed new cuprophan dialyzer.

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Table 1
Methods of pretreatment for the first
and subsequent uses of the dialyzer

Manual method (1981-1983)	Automated (DRS-4) method (1984-1985)
1. Warm treated water rinse of blood and dialysate compartments for 10 min.	1. Full DRS-4 reuse cycle: a. Warm water rinse of blood and dialysate compartments. b. Reverse ultrafiltration with water. c. Bleach fill and back ultrafiltration. d. Warm water rinse.
2. Tests: Total bundle volume	2. Tests: KUF Total bundle volume Fiber leak rate
3. Blood and dialysate compartments filled with 1.5% formaldehyde.	
4. Dialyzer is labelled and stored for 36 hours before use.	
5. Prior to use dialyzer rinsed with 1000 ml normal saline and recirculated for 10 min.	5. Prior to use dialyzer rinsed with 400 ml normal saline and recirculated for 10 min.

From Charoenpanich R, et al. Artificial Organs (in press) 1985

Table 2

Incidence of complications affecting the patient and occurring during dialysis in periods in which the dialyzers were processed manually or by machine

Complication	Manual Processing			Machine Processing		
	First Use (n=4933)	All Other Uses (n=21,659)	$\chi^2_{[1]}$	First Use (n=1037)	All Other Uses (n=11,358)	$\chi^2_{[1]}$
	(%)	(%)		(%)	(%)	
Hypotension	34.0	28.6	56.0****	34.7	39.2	8.0***
Cramps	19.0	14.8	53.8****	16.5	13.3	8.0***
Nausea or Vomiting	13.8	11.9	13.6***	13.0	13.8	NS
Headache	4.1	3.4	5.8**	4.0	3.3	NS
Itching	3.3	2.4	15.0****	2.4	1.5	4.8*
Chest Pain	4.9	1.7	174.7****	1.5	1.3	NS
Back Pain	3.6	0.6	311.8****	0.8	0.7	NS
Pain Elsewhere	4.2	2.9	24.7****	3.2	2.0	7.3***
Dyspnea	0.6	0.2	22.8****	0.4	0.3	NS
Chills	0.5	0.2	16.5****	0.3	0.3	NS
Tremor	0.2	0.08	9.2***	0.1	0.2	NS

* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$; **** $p < 0.001$

Reprinted, slightly modified, with permission from Charoenpanich,R. et.al. Artificial Organs (in press) 1986

Table 3
Incidence of selected complications occurring
during the first and subsequent use of dialysers
processed manually or by machine

Complication	Dialyzer Processing			
	Manual		Machine	
	First Use (n=4933)	All Others (n=21,659)	First Use (n=1037)	All Others (n=11,358)
	(%)	(%)	(%)	(%)
Chest Pain	4.9	1.7	1.5	1.3
Back Pain	3.6	0.6	0.8	0.7
Chest and back pain	1.16	0.027	0.1	0

Table 4

Incidence of a severe syndrome occurring
with the first use of hemodialyzers
by type of dialyzer and membrane

Membrane Type	Three Dialysis Units Chicago (1973-1983)*		Dialysis Clinic Cincinnati (1977-1985)**	
	(#)	(#/100,000)	(#)	(#/100,000)
		Hollow fiber dialyzers		
Regenerated cellulose	0/69,994	0	0/9180	0
Cuprammonium cellulose	19/33,510	56.7	3/4200	71.4
Saponified cellulose ester	0/ 2,089	0	0/1536	0
Cellulose acetate	0/50.762	0	0/158	0
		Plate dialyzers		
Cuprammonium cellulose	2/54.531	3.7	NA	NA
Polyacrylonitrile	0/ 2,788	0	NA	NA
		Coil dialyzers		
Cuprammonium cellulose	0/46.753	0	NA	NA

* Daugirdas JT, et al., Arch. Int. Med. 145:489, 1985.

** Kant KS, et al., Kidney Int. 19:728, 1981;
Robson MR et al. Am. J. Nephrol. (in press), 1985;
Charoenpanich R, et al., Artificial Organs (in press), 1986.
Stock records, Dialysis Clinic.

Table 5

Some characteristics of mild and severe syndromes occurring during the first use of hemodialyzers

	Mild Syndrome*	Severe Syndrome**
Clinical	Chest and back pain	"Hypersensitivity"
Incidence	0.1 - 1.16%	0.057%
Type of dialyzer	Hollow fiber	Hollow fiber
Type of membrane	Regenerated cellulose Saponified cellulose ester Cuprophan	Cuprophan
	Relative Incidence	
Race (Black:White)	0.7:1	2.8:1
Sex (Male:Female)	0.2:1	1.0:1
Age (<30:>30)	0.3:1	2.1:1

*Robson MD, et al. Am J Nephrol (in press) 1985; Charoenpanich R, et al. Artif Organs (in press).

**Daugirdas JT, et al. Arch Int Med 145:489, 1985; Villarroel F, et al. Artif Organs 9:231, 1985.

Table 6

Incidence of a severe syndrome associated with the use of cuprammonium cellulose hollow fiber hemodialyzers at Dialysis Clinic, Cincinnati

Dialyzer Use	Dialyses*	Severe Reactions	Rate
	(#)	(#)	(#/100,000)
All uses	42,000	3	7.14
Second and subsequent use	37,800	0	0
Initial use, all methods of dialyzer preparation	4,200	3	71.4
Initial use, dialyzers preprocessed	3,700	0	0
Initial use, "dry pack" dialyzers, saline rinsed	500	3	600

*Numbers are approximate numbers for each type of dialyzer preparation.

(NOTE: THIS DOCUMENT WAS INCLUDED IN THIS RECORD AT THE REQUEST OF SENATOR LARRY PRESSLER, MEMBER OF THE SPECIAL COMMITTEE ON AGING.)

HEMODIALYZER REUSE IN END-STAGE RENAL DISEASE NETWORK 7:

Assessment of current practices, revised Network 7 standards and recommendations for compliance

Report of the Hemodialyzer Reuse Task Force:

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May, 1985

Approved June 1985 for use in
ESRD Network 7
Medical Review Board
Renal Network Coordinating
Council of the Upper Midwest

Report of the End Stage Renal Disease Network 7 Hemodialyzer Reuse Survey

A survey was performed to determine the practice of hemodialyzer reuse in the 31 facilities of ESRD Network 7 one year after the National Kidney Foundation (NKF) issued "Revised Standards for Reuse of Hemodialyzers." Specific questions to be answered were:

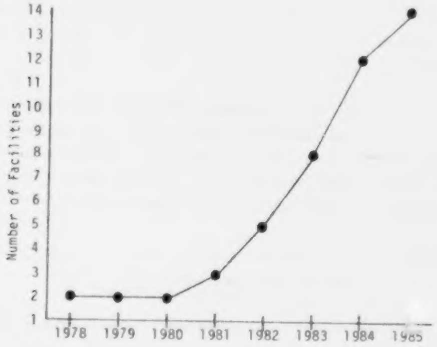
1. What is the current practice of hemodialyzer reuse in Network 7?
2. How does the practice of hemodialyzer reuse in Network 7 conform to, or vary from, the NKF Revised Standards?
3. Are the deviations from the recommended standards of a nature potentially dangerous to patients or staff?
4. What are the implications of implementing the NKF Revised Standards within Network 7?

BACKGROUND

The first standards for the practice of hemodialyzer reuse, "The Interim Standards for Reuse of Hemodialyzers" were established by the NKF in June 1982. These were adopted by the Medical Review Board of Network 7 on May 5, 1983. In December 1983, following the 1982 outbreak of a non-tuberculosis mycobacterial infection among patients in two centers which used dialyzers disinfected with formaldehyde at a central facility, the NKF issued "Revised Standards for Reuse of Hemodialyzers." The major revisions were an increase in the minimum concentration of formaldehyde from 2% to 4% in both the blood and dialysate compartments and an increase in the minimum exposure time for disinfection from 16 to 24 hours. These were in keeping with the recommendations from the Center for Disease Control (CDC) which had found this non-tuberculous mycobacterium to be resistant to formaldehyde at lower concentrations for shorter durations of exposure.

Within Network 7, the practice of hemodialyzer reuse was initiated in one facility in 1978. In 1981 a second facility began, and the practice of reuse began to increase dramatically (Figure 1). By January 1985, in the 31 facilities providing chronic care to 967 patients in Network 7, 45.2% of facilities serving 68.8% of Network 7 patients were participating in hemodialyzer reuse. By comparison, 16% of dialysis patients nationally participated in hemodialyzer reuse in 1978. By 1981, this increased to 27.5% of patients; by January 1983, 43% of the facilities and 51% of the patients in the United States were utilizing hemodialyzer reuse.

Figure 1: Number of Network 7 Dialysis Facilities Performing Dialyzer Reuse, 1978-1985



METHODOLOGY

The NKF Revised Standards (Appendix A) provided the framework for a questionnaire (Appendix B) developed to assess dialyzer reprocessing procedures in Network 7 facilities. This questionnaire was mailed to the medical directors of the facilities on January 9, 1985 to be filled out by appropriate individuals. General categories of the questionnaire included: Reuse methods and disinfectants, safety of technical staff, dialyzer individualization, dialyzer safety, esthetic appearance and criteria for discarding reused dialyzers, dialyzer effectiveness, dialyzer disinfection, consent for reuse, indications for reuse or reservations regarding reuse, and types of dialyzers being reused. The patient census of specific facilities and the current hepatitis status were provided by the Network.

FINDINGS

Questionnaires were returned by all facilities between January and April 1, 1985. Of 31 facilities reporting, 11 indicated that they do not reuse dialyzers nor do they plan to begin reuse, six are not currently reusing, but plan to begin reuse in the future, and 14 facilities are currently reusing dialyzers.

Fourteen questionnaires from reusing facilities were tabulated; nine were completed by a registered nurse in the unit, three were completed by the *in vitro* laboratory manager, one was completed by the unit technical supervisor, and one by the physician medical director.

The results of the questionnaire indicate that three of fourteen Network 7 units practicing reuse were unaware of any NKF standard despite its adoption by the Medical Review Board in 1983. Of the 11 units familiar with the Revised Standard, five reported compliance with the recommendations. As detailed below, no units in Network 7 are currently in compliance with all recommendations.

The findings discussed below are organized around the four basic questions of the survey. The first two questions are addressed together.

1. What is the current practice of hemodialyzer reuse in Network 7?

2. How does the practice of hemodialyzer reuse in Network 7 conform to, or vary from, the NKF Revised Standards?

REUSE METHODS AND REUSE DISINFECTANTS

All units practicing reuse employ automated systems. Eleven use a Renatron^{TM}, and two use the device manufactured by Seratronics^{TM}. One facility currently using the device manufactured by Compudial^{TM} plans to switch to a Seratronics^{TM} machine.

Five units use formaldehyde, and nine units use the Renalin^{TM} formulation of peracetic acid as the disinfectant. Two units using formaldehyde plan to switch to peracetic acid.

SAFETY OF TECHNICAL STAFF

As recommended by the NKF Standards, all units provide:

- a. suitable, discreet space for reprocessing and storing used dialyzers;
- b. written protocols and training for safe handling of toxic substances;
- c. procedures for spills and splashes of toxic substances;
- d. devices for protection from toxic substances.

Eleven of the reusing facilities control and monitor toxic fumes to meet Occupational Safety and Health Administration (OSHA) Standards. Of the three not monitoring fumes, two use peracetic acid as the disinfectant, and the third plans to switch from formaldehyde to peracetic acid.

DIALYZER INDIVIDUALIZATION

In compliance with the NKF Standards, 13 of 14 facilities label reused dialyzers with the patient's name and other unique identifying information. One labels only with the patient's name. In all units, the label is checked by two separate individuals at each use, and the number of uses is recorded both in a record maintained for the dialyzer and in the patient's dialysis record.

Thirteen of 14 facilities exclude patients with hepatitis B antigenemia from reuse in compliance with NKF Standard. Four units indicated that they had no patients who were hepatitis B antigen positive. Five units indicated on the 1984 Centers for Disease Control (CDC) Hepatitis Survey that they did treat hepatitis B antigen positive patients in 1984.

DIALYZER SAFETY

The NKF Standards prescribe that water used to formulate cleaning solutions and to rinse dialyzers should be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter (0.45 micron). Twelve of 14 facilities are in compliance with this recommendation. Eleven facilities use a reverse osmosis membrane and one facility uses deionization followed by a suitable filter. A single unit uses water which is treated by softening only, and a second uses water treated by deionization but without a 0.45 micron filter or ultrafiltration membrane.

All units report doing bacteria counts at least monthly in compliance with the NKF Standard, and 12 specified that their upper permissable limit for bacteria was less than 200 colonies per milliliter. One unit did not specify its permissable level and one unit specified that the count must be equal to or less than 250 bacterial per milliliter. Seven units indicate that their testing is done by the Millipore Total Count Sampler^{TM}.

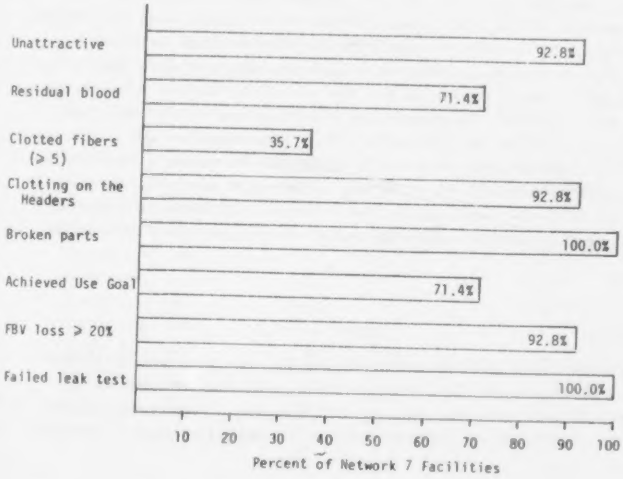
The NKF Standard requires that reuse water contain a level of bacterial endotoxin of less than 1 nanogram per milliliter which is documented by Limulus amoebocyte lysate (LAL) testing not less than monthly. Only four units indicate compliance with this recommendation. It is noteworthy that the units which did not have either an ultrafiltration membrane or a 0.45 micron filter also do not perform LAL testing.

The NKF Standard requires maintenance of a log of all febrile reactions during dialysis and a written procedure, including blood and dialysate cultures, during all febrile reactions. Ten facilities indicate that they maintain such a log with eight facilities having a written procedure which includes appropriate cultures. Thirteen facilities indicate that they maintain the recommended log for blood leaks. Twelve facilities maintain a record of patient reactions to disinfectant, however, only two facilities indicate that they have physician's orders for dealing with such reactions.

ESTHETIC APPEARANCE AND CRITERIA FOR DISCARDING REUSED DIALYZERS

All units discard dialyzers which were either broken on visual inspection or which failed a pressure test (Figure 2). Nearly all units (92.8%) discard the dialyzer if it was unattractive, had clotted headers or had a loss of fiber bundle volume equal to or greater than 20%. Most (71.4%) units discarded dialyzers which were discolored by residual blood or which had reached a predetermined number of uses. Only 35% of the facilities discarded dialyzers that had five or more visible clotted fibers after reprocessing. This criterion, however, relates only to units which use formaldehyde as a disinfectant because peracetic acid bleaches even clotted fibers white.

Figure 2: Criteria for Discarding Reused Dialyzers



DIALYZER EFFECTIVENESS

The NKF Standard recommends that "validation studies including at least in vivo or in vitro clearances of creatinine and urea and ultrafiltration rate of each dialyzer type reprocessed by a facility should be conducted not less than quarterly." Only one facility indicated compliance with this recommendation by monthly in vivo testing. A second facility performs in vivo testing every six months and a third facility indicated performance of in vitro testing whenever a new dialyzer or reuse procedure was initiated.

DIALYZER DISINFECTION

Of 14 facilities practicing reuse, five use formaldehyde as a disinfectant, and nine use peracetic acid as disinfectant. Of the five facilities using formaldehyde, three facilities report adding 4% to both the dialysate and blood compartments, while two indicate storage concentration in both compartments of approximately 2.5%. The manufacturer's specifications indicate that not all the machines in use in those sites are able to deliver a 4% concentration of disinfectant to both compartments. Consequently, some of the facilities which utilize formaldehyde are not in compliance with the NKF recommendations. To date, the NKF has not recommended a concentration standard for peracetic acid. The manufacturer of peracetic acid indicates that a concentration of 750 mg/l and a contact time of 11 hours will effectively disinfect reused dialyzers provided that other requirements for its application are also met.

CONSENT

The NKF Standard states that informed consent for the reuse procedure is essential and that if patients do not sign a consent form to reuse, they are entitled to a new dialyzer for each treatment. Only one unit in Network 7 reports that consent for reuse is not obtained and that participation in hemodialyzer reuse is mandatory.

REASONS FOR REUSE AND RESERVATIONS ABOUT REUSE

In describing reasons for reuse, 92.8% of units listed economic considerations, 42.8% of units indicated a reduced incidence of first-use syndrome, 37.7% of units indicated that patients feel better and 7% of the units did not respond.

The one reservation about reuse, a concern about the long-term effects of exposure to disinfectants by both patients and staff, was listed by 57% of the units. Four units (28.5%) indicated that they had no reservations, and one unit questioned whether reuse is cost effective and expressed reservations regarding the related volume of record keeping required.

TYPES OF DIALYZERS REUSED IN NETWORK 7

The types of dialyzers used, the average number of uses and the range and number of units using a particular brand of dialyzer are shown in Table 1.

Table I
Hemodialyzer Reuse Network 7 by Dialysis Type

	Number of Uses		Number of Facilities Reusing This Type
	Mean	Range	
Travenol CF 1211	7.9	4-15	12/14
Travenol CF 1511	7.7	4-12	12/14
Travenol CF 2308	7.0	6- 8	2/14
Cordis Dow 90	6.0	--	1/14
Cordis Dow 135	6.0	--	1/14
Cordis Dow 3500	6.0	4-10	3/14
Cordis Dow 4000	5.0	4- 8	5/14
TAF 10	5.8	4-12	4/14
TAF 12	8.0	6-12	3/14

3. Are the deviations from the recommended standards of a nature potentially dangerous to patients or staff?

The survey has revealed several deviations from the Revised Standard. Four (VI, VII, VIII, IX) are considered highly significant and prompt corrective action is recommended. We will discuss each deviation in terms of the purpose of the standard, potential clinical significance of noncompliance, and recommendations for action.

I. Failure to label each used dialyzer with the patient's name and other unique identifying information. Units involved: 1.

The purpose of requiring two forms of identifying data is to minimize the risk of patients with similar names receiving another individual's dialyzer. Even with two labels, dialyzer mix-up occasionally occurs. Although no adverse reactions have been reported from this, it is certainly to be avoided.

RECOMMENDATION: Compliance for all units. This is a quick, easy, inexpensive process to implement that may prevent dialyzer mix-up.

II. Failure to maintain a log of febrile reactions during dialysis and
III. Failure to maintain written protocols, including blood and dialysate cultures during febrile reactions. Units involved: 4 and 6 respectively.

The purpose of this standard is to provide an epidemiologic monitor for disinfection as a signal to reevaluate the reuse procedure if febrile reactions with reused dialyzers exceed those seen with new dialyzers.

RECOMMENDATION: Complete compliance. Logs of febrile reactions and a protocol for appropriate cultures are easily implemented in all settings.

IV. Failure to perform quarterly validation studies of dialyzer performance. Units involved: 13.

The purpose of this standard is to ensure that patients are treated with dialyzers which though reused, perform to expected specifications for diffusion and ultrafiltration. All facilities in Network 7 currently use commercial, automated reuse devices, and no facility is performing manual reuse. It is our opinion that the need for performance testing is greatly diminished with automated systems as manufacturers imply adequate performance if conditions for installation, operation and dialyzer discard are met. The need for validation testing may be further diminished if patients are carefully monitored by serum chemistries at least monthly and if variations in these chemistries are systematically evaluated. Systematic evaluation would include verification of adequate blood and dialysate flow rates as well as studies to assess access recirculation in addition to dialyzer performance. To require quarterly testing in the setting where patient chemistries are routinely monitored and documented to be stable and where appropriately maintained automated reuse procedures are followed is probably excessive.

RECOMMENDATION: Validation testing is probably unnecessary on a quarterly basis where automated systems are used unless changes in patient chemistries and/or fluid status indicate need for review of these parameters.

V. Failure to exclude patients who are hepatitis B antigen positive from hemodialyzer reuse. Units involved: 1.

The purpose of this recommendation is to minimize risk of transmitting hepatitis to dialysis staff or other antigen negative patients.

RECOMMENDATION: Complete compliance with this regulation unless:

a. All hepatitis B antigen positive patients are treated in an isolation area distinctly separate from antigen negative patients and which includes separate dialysis delivery systems.

b. Vaccination with Heptavax be recommended and provided for all antigen negative patients and staff and the efficacy of vaccination be documented by antibody testing.
c. Dialyzers from antigen positive patients be reprocessed in an area separate from that used for reprocessing dialyzers from antigen negative patients.
d. That a separate automated reuse device be used only for patients who are hepatitis B antigen positive.

Unless a facility treats a large number of antigen positive patients, it will not be cost effective to operate a separate unit and reprocessing area for these individuals. It is noteworthy that with application of routine screening tests for the hepatitis B surface antigen, the strict isolation of antigen positive patients, and the vaccination of antigen negative individuals, new cases of hepatitis B have been virtually eliminated. In 1984, only 2 new cases of hepatitis B were reported and a total of 17 antigen positive patients were treated in 28 Network 7 facilities which completed the CDC Hepatitis Survey.

By contrast, 15 new cases of non-A, non-B (NANB) hepatitis were reported by these Network 7 facilities in 1984. It seems certain that NANB hepatitis either is, or soon will be, the major hepatitis in the dialysis setting. The risk of developing NANB hepatitis after receipt of a single unit of blood has been reported to be as high as 7%. Considering that 5 to 10 units of blood are now recommended for younger patients prior to transplantation and that the number of elderly patients with organic heart disease who receive transfusions to control angina is increasing, the potential for significant numbers of patients developing NANB hepatitis is readily apparent. Since definitive diagnostic tests or uniform diagnostic criteria for NANB hepatitis are unavailable, patients suspected of having NANB hepatitis should be excluded from hemodialyzer reuse.

VI. Failure to treat water for reuse with a reverse osmosis membrane, ultrafiltration membrane or 0.45 micron filter; and

VII. Failure to document a level of bacterial endotoxin of less than 1 nanogram per milliliter monthly. Units involved: 1 and 10 respectively.

The purpose of this guideline is to control the load of bacteria presented to the dialyzer which must be eradicated by the disinfectant and to document low levels of endotoxin which may contribute to pyrogen reactions during dialysis. These standards require users to control both bacteria _and_ pyrogen. Therefore, it is important to note that a reverse osmosis membrane or ultrafiltration membrane can remove both bacteria and pyrogen, while a 0.45 micron filter will only remove bacteria. Ultrafiltration membranes have a higher initial cost than the 0.45 micron filter, however, they are reusable for extended periods of time and have superior organic filtration characteristics. LAL testing is modest in cost and of considerable potential benefit.

RECOMMENDATION: Compliance with LAL testing.
Compliance with NKF water treatment standard with strong encouragement for the use of ultrafiltration membranes rather than the 0.45 micron filter which is also acceptable.

VIII. Failure to use 4% formaldehyde in both the blood and dialysate compartments. Units involved: 3 (and possible more, depending on the reuse device utilized)

The purpose of this recommendation is to avoid a second outbreak of nontuberculous mycobacterial infection as occurred in Louisiana. The Louisiana outbreak involved 24 patients, 13 of which died. While the extent to which the mycobacterial infection contributed to their deaths in unknown, it would be indefensible to ignore the CDC/NKF recommendation for 4% formaldehyde in light of this data.

The risks of outbreaks such as occurred in Louisiana exist whenever formaldehyde is used in concentrations of less than 4% and are increased if this is coupled with the use of inadequate water purification systems. A further liability of these circumstances is that conventional bacterial culture techniques, including the Millipore Total Count Sampler™, are incapable of detecting the atypical mycobacteria which have the potential for formaldehyde resistance. Moreover, water supplies which do not presently contain such organisms cannot be relied upon to remain so in the future.

RECOMMENDATION: Strict compliance; i.e. if formaldehyde is used, it must be added to a minimum concentration of 4% in both compartments of the dialyzer with an exposure time of 24 hours. Facilities using formaldehyde should document a 4% concentration in the dialysate and blood compartments by testing through an independent laboratory or other suitable technique at initiation of the system and every six months thereafter.

IX. Failure to monitor potentially toxic fumes to OSHA levels. Units involved: 3.

The purpose of this standard is to protect both patients and dialysis personnel from exposure to toxic levels of disinfectants.

Two disinfectants, peracetic acid and formaldehyde, are currently employed for dialyzer reuse in Network 7. An OSHA standard is available only for formaldehyde fumes. Although not covered in the survey, units may use formaldehyde for disinfecting delivery systems, water systems, etc., which would also require monitoring.

For facilities in the State of Minnesota (9/14) compliance with the Minnesota Employees Right to Know Act (MERTKA) of 1983, which also addresses issues of chemical monitoring and safety, is mandatory and not simply a recommendation.

RECOMMENDATION: Compliance with both OSHA and, where applicable, MERTKA regulations.

4. What are the implications of implementing the NKF Revised Standards for Hemodialyzer Reuse within Network 7?

Except as previously noted within this report, compliance with the NKF Interim Standard within Network 7 is relatively high. This standard, which has been endorsed by the Network Medical Review Board, has been revised by the NKF to reflect and recommendations of the CDC, the use of formaldehyde at lower concentrations must be considered unacceptable.

In addition to the present NKF Revised Standard, similar standards have been or are being developed by other ESRD Networks, some states and the Association for the Advancement of Medical Instrumentation. The latter, which is still under development, will be more extensive than any yet seen.

Our recommendation to the Network at this time is to endorse the NKF Revised Interim Standard with the following modifications:

1. Validation studies of dialyzer performance are necessary only if changes in patient's chemistries or fluid status indicate such a need providing that
    a. properly installed and maintained automated reuse systems are employed and operated according to the manufacturer's instructions, and providing that
    b. patient fluid status and chemistries be carefully monitored (at least monthly) and documented to be stable and satisfactory.
2. Patients who are hepatitis B surface antigen positive may participate in hemodialyzer reuse if all conditions listed on p. 10-11 are met. Patients suspected of having NANB hepatitis should be excluded from hemodialyzer reuse.
3. All facilities are strongly encouraged to use reverse osmosis or ultrafiltration membranes as part of the treatment for reuse water.
4. The requirements for dialyzer reuse in the home should be separately developed as those of the NKF cannot be practically implemented.
5. The Network administration should ensure a complete flow of information concerning its reuse position to facilities' physician, nursing and technical staffs. This recommendation is made because three facilities practicing reuse in Network 7 were not aware of the NKF Standard.
6. The Network should consider providing professional and/or technical assistance to facilities either reusing or contemplating reuse.

Item 9

Reuse Of Hemodialysis Devices: Chronology Of Major Events

1898 - 1986

Prepared by the staff of the Special Committee on Aging

REUSE OF HEMODIALYSIS DEVICES:

CHRONOLOGY OF MAJOR EVENTS

1898 Dr. Hansen, a scientist, produced liver damage (hepatoxicity) in cats by injecting 4% formalin (formaldehyde) into the gall bladder of cats. [NOTE: FORMALDEHYDE IS THE CHEMICAL MOST OFTEN USED AS THE "DISINFECTANT" IN THE REPROCESSING OF DIALYSIS DEVICES, DIALYZERS, BLOOD LINES, ETC.]

1905 Dr. Fischer, a scientist, conducted the first "systematic studies of the hepatotoxicity" (liver damage causing) of formaldehyde and confirmed the findings of Dr. Hansen (see above) and earlier findings of others. [NOTE: A NUMBER OF OTHER TOXICITIES ASSOCIATED WITH FORMALDEHYDE HAVE BEEN IDENTIFIED SINCE THE TURN OF THE CENTURY; THEY INCLUDE, BUT ARE NOT LIMITED TO, CANCER-CAUSING, KIDNEY DAMAGE-CAUSING, ASTHMA-CAUSING, TERATOGENIC (BIRTH DEFECTS), INTERFERENCE WITH REPRODUCTIVE ACTIVITIES, INTERFERENCE WITH THE CENTRAL NERVOUS SYSTEM AND DAMAGE TO BLOOD (IMMUNOLOGICAL).]

10/30/72 P.L. 92-603 established Medicare funding of dialysis under the End Stage Renal Disease Program (ESRD).

11/11/77 FDA Compliance Policy Guide 7124.23, Chapter 24 - Devices. SUBJECT: Reuse of Medical Disposable Devices. ". .[T]here is a lack of data to support the general reuse of disposable medical devices *** [T]he institution or practitioner who reuses *** should be able to demonstrate: (1) that the device can be adequately cleaned and sterilized, (2) that the *** quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use.***FDA considers disposable devices which are being reused, and which have not been demonstrated to be capable of complying with the requirements in the above [sentence], to be adulterated *** and in violation of 21 U.S.C. 331(k). [SEE FDA'S REVISED 7/1/81 COMPLIANCE POLICY GUIDE BELOW.]

6/13/78 P.L. 95-292: "Special Provisions Relating To Coverage Under Medicare Program for [ESRD]. This law mandated a study by NIH of reuse of dialyzers to determine safety. [SEE 10/17/78 ENTRY BELOW.]

10/17/78 Research Concept Clearance. Project Title: Study of Dialyzer Reuse. Project Officer: Robt. Wineman, Ph.D. "Factors to be evaluated will include evaluation of multiple resterilization *** procedures, bacteriological and virological safety and patient response factors especially, immunologic and antigenic.***Reuse of [dialyzers] has been a topic of interest and concern [for] over fifteen years.***Because of the potential cost savings with reuse, Congress recently passed Public Law 95-292 which requires "The Secretary shall conduct a study of the medical appropriateness and safety of cleaning and reusing dialysis filters by home dialysis patients.***A coordinated plan for determining the medical appropriateness and safety of reuse is under development by NIH, FDA and CDC. If reuse is considered appropriate, changes in dialyzer labeling will be required (FDA) and possibly changes in ESRD regulations under Medicare (HCFA).

10/20/78 Memo to Administrator, HCFA, from Asst. Secretary for Health and Surgeon Geneeral. RE: Coordination of a Work Plan for Studies on End-Stage Renal Disease (ESRD) - INFORMATION. ". . [S]tudies listed in P.L. 95-292 for ESRD should be started or evaluated quickly.*** The Public Health Service (PHS) expects to be reimbursed by HCFA for all research performed by PHS in this regard.*** PHS concurred with projected funding estimates developed by the FDA and NIH. ."

1/15/79 Memo to Asst. Secretary for Health and Surgeon General from Administrator, HCFA. RE: Coordination of Experiments and Studies on ESRD Authorized by P.L. 95-292; Your memo of Oct. 20. ". . [W]e expect that the costs of administering and evaluating the studies and experiments will be funded by the respective agencies with lead responsibility, as outlined in our memo of Sept. 8. HCFA is planning to request a supplemental appropriation to cover the necerssary costs of carrying out studies and experiments [other than dialyzer reuse].*** We expect the [PHS] to arrange for obtaining funds to conduct studies of *** the medical appropriateness of dialyzer reuse.***"

5/20/79 >"DIALYZER REUSE: Napht's Statement of Position" position paper adopted by the Board of Directors of the National Association of Patients on Hemodialysis and Transplantation, Inc. "NAPHT is opposed to the reuse of disposable hemodialysis filters at the present time except in carefully planned and controlled experimental situations where patients elect to participate in the study.***The patient being asked to reuse dialyzers should be informed of the possible side effects, of expected number of uses, and of the methods and controls on reprocessing.***Until such time as dializer reuse is proven to be safe and effective (by careful scientific study as well as by clinical observation), NAPHT is opposed to this practice."

6/80 "Investigation of The Risks And Hazards Associated with Hemodialysis Devices" report, prepared for FDA, Bureau of Medical Devices (Kobren et al.), by the Regional Kidney Disease Program, Minneapolis Medical Research Foundation. This study had two goals: ". . to provide [FDA] with the information required for writing and implementing standards; [and] to provide *** additional data [for] evaluation of system component devices.***The study's scope was restricted to device performance relative to patient safety.***The principal justification for reusing dialyzers is an economic one.***The safety and efficacy of reuse is a subject of some controversy. [S]ome reports *** document the adverse effects of reuse, [but] others *** indicate that dialyzer reuse is safe and effective *** with minimal patient complications.***[The Health Industry Manufacturers' Association (HIMA)] appropriately points out that *** the practice of reuse is largely unregulated and therefore does constitute a potential threat to patient safety.***The issue to be resolved *** is whether standards, either performance or disclosure, can be written for the reuse of dialyzers. At the present time, such standards cannot be proposed for two reasons: First, in the absence of definitive studies, such as the one contemplated by the NIH, the necessary criteria to establish standards cannot be formulated. Second, at the present time, manufacturers label dialyzers *** for single use only. Unless these issues are resolved, standards related to reuse are not relevant. ."

1/5/81 Memo to ASH, DHHS, from Jere Goyan, M.D., FDA Commissioner. RE: reuse of dialyzers--a response to 11/18/80 ASH inquiry about reuse. ". . The guide [compliance policy guide?] is intended to address responsibility for reuse *** when such action is clearly contrary to the mfgr's labeling.***When an institution *** chooses to reuse *** the responsibility ***shifts from the mfgr. to the party responsible for the reuse.***The enclosed document, 'Reuse of Disposable Hemodialyzers', prepared in April 1979, still represents FDA's opinion--that is, that FDA cannot at this time recommend the reuse of [dialyzers].***The studies *** under way at the [NIH] will *** be concluded in December 1980. These may affect *** reuse; in the event that the NIH studies change our current position, we will advise you. In any case we do not believe there would be any significant change in FDA's position on the question of responsibility under the FD & C Act."

1/7/81 Lttr to E. L. Kelly, Acting Dir., Office of Special Programs, HCFA, from Nancy B. Cummings, M.D., Assoc. Dir., NIAMDD, NIH, and Robert Wineman, Ph.D., Program Dir., Chronic Renal Disease Program, NIAMDD, NIH. RE: research and/or demonstrations relating to ESRD. ". . In some cases the fundamental research contribution [of these projects] to medical science would be fairly low. With this factor in mind,*** it would be relatively unlikely that NIH would fund some types of research that might have great interest to HCFA because of its economic impact.*** Clinical Trial of Multiple Use of Hemodialyzers***[would have] a significant economic impact but a low contribution to basic medical science. Potential cooperation from HCFA: (a) Full funding of the needed clinical trials***. (b) Supervision of collection of data on cost and material manpower required for multiple use. (c) Contributions to design of the overall study. ."

1/15/81 Memo to Dr. Nancy Cummings, Dir., NIAMDD, NIH, and James Kaple, Dir. ORDS, HCFA, from Ronald Schwartz, Acting Asst.

IG for Health Care and Systems Review. RE: Request for Info on Kidney Dialyzer Reuse Research. "It has come to our attention that [NIAMDD] had discontinued *** research efforts into the efficacy and safety of kidney dialyzer reuse. Under the 1978 Amendments to the [SSA], Congress mandated *** this research *** Now it appears unclear whether [NIH] or [HCFA] is primarily responsible for financing and administering the continuation of dialyzer research beyond Phase I.***Unless HCFA and NIH can *** resolve this issue, we plan to notify the Congress.***We request that a formal, written explanation which outlines your position on this issue be returned to this office [by] January 27, 1981." [SEE 8/17/84 DHHS OIG LTTR BELOW.]

1/28/81 Memo to Acting Asst. IG, Health Care and Systems Review, DHHS, from Nancy Cummings, M.D., Associate Dir., NIAMDD, NIH. ". . No funds were made available for dialyzer reuse studies, nor was responsibility assigned formally to any PHS Agency.***[In] 1979, because no funds were available and because these studies were not deemed to be scientific research, the decision was made to limit an award to a one-year pilot study by contract.***[Dr. James Kaple of HCFA and I] concur that since the issue about dialyzer reuse is one of SAFETY of dialyzer reuse, it would appear to belong more appropriately within FDA's sphere of responsibilities. ."

2/81 Memo to R. D. Schwartz, Acting Asst. IG for Health Care & Systems Review, from James Kaple, Acting Dir., Office of Research, Demonstrations and Statistics, HCFA. RE: Response to Your Request For Information Pertaining to Kidney Dialyzer Reuse. ". . P.L. 95-292 mandated *** a study on the medical appropriateness and safety of cleaning and reusing dialysis filters by home dialysis patients.*** The Department divided responsibility *** between HCFA and PHS.*** PHS indicated [see 10/20/78 memo above] that they expected to be reimbursed by HCFA for all research pertaining to their responsibilities under the legislation. HCFA responded to PHS [see 1/15/79 memo above] that we expected PHS 'to arrange for obtaining funds to conduct studies'***. PHS did not respond to this memorandum***."

4/2/81 Memo to Ronald Schwartz, Acting Asst. IG for Health Care & Systems Review, DHHS, from Acting Dir., Bureau of Medical Devices, FDA. RE: response to Schwartz 2/25/81 memo (ABOVE) on dialyzer reuse. ". . The FDA disagrees with with Dr. Cummings' (NIH) statement that the responsibility for conducting dialyzer reuse research *** would appear to belong *** within FDA's sphere of responsibilities.***The FDA position on reuse *** is in a January 5, 1981 memo from the Commissioner *** to the Assistant Secretary for Health: 'When an institution or practitioner chooses to reuse a single-use [dialyzer] the responsibility for the safety and effectiveness of the reused device shifts from the manufacturer to the party responsible for the reuse.' A well-designed clinical study addressing the overall safety of reuse versus single-use might be desirable, however, such a study is not within the mission of the FDA. Such research should be performed by agencies equipped and staffed for research activities." [SEE 1/5/81 FDA COMMISSIONER MEMO TO ASH ABOVE.]

4/9/81 Memo to Nancy Cummings, M.D., Dir., Kidney, Urologic and Blood Disease, NIH, from Edward Kelly, Acting Dir., Office of Special Programs, HCFA. RE: multiple use of dialyzers. ". .[A] medical practice *** employed for 20 years *** cannot be considered experimental.***[W]e believe there is sufficient evidence to make a decision that reuse is a generally safe, efficacious, and cost effective procedure when appropriate standards are met for reprocessing *** The single most important issue *** is the *** promulgation of standards including criteria for patient selection.***[S]uch standards would be most effective if they were consensus standards, developed by all involved governmenmt agencies--the NIH, CDC, FDA and HCFA. Therefore, we recommend that you call a meeting upon the receipt of Dr. Deane's study . ." [NOTE: THIS MEMO WAS PREPARED BY HSQ, OSP, OESRD, HCFA; SEE 5/16/81 NIH MEMO BELOW.]

4/15/81 Lttr to Dr. Seymour Perry, Dir., Nat'l Center for Health Care Technology, DHHS, from Robt. Wineman, Ph.D., Program Dir., Chronic Renal Disease Program, NIADDKD, NIH. RE: Comments on the ESRD Program Evaluation Plan. ". . The NIH study has been confined to being a laboratory feasibility study to demonstrate that a reprocessed dialyzer has performance characteristics which are essentially in the same range as a new dialyzer. The NIH study did not undertake a longer term examination of any clinial factors including adverse patient responses during therapy nor any measures of immunological response.***In the NIH study, the attempt was made to show that performance characteristics of reprocessed dialyzers, residual sterilant content, and sterility status are in reasonable ranges to use reprocessing techniques. ." [SEE 1/15/81 DHHS OIG MEMO AND 1/28/81 NIAMDD, NIH, MEMO ABOVE.]

4/23/81 Lttr to Norman Deane, M.D., Nat'l Nephrology Foundation (NNF), from John Ketteringham, Vice President, Arthur D. Little Inc. (ADL) RE: Ketteringham's request to review the report on the NIH funded study prior to publication [ADL WAS THE SUBCONTRACTOR TO NNF FOR RESEARCH ON REUSE OF DIALYZERS]. "As we agreed, I would appreciate the opportunity to review and contribute to the final version [of the report] before it is published***." [NOTE: SEE 6/30/81, 5/4/81, 10/7/81, 10/9/81 & 3/19/82 ENTRIES BELOW.]

5/4/81 Lttr to John Ketteringham, Arthur D. Little Inc., from Norman Deane, M.D., Nat'l Nephrology Foundation, Manhattan Kidney Center. "Your letter [of 4/23/81] suggests a misunderstanding since I did not agree *** to give you review prerogatives on the final report [concerning reuse of dialyzers]***." [NOTE: SEE 4/23/81 ENTRY ABOVE, AND 6/30/81, 10/7/81, 10/9/81 & 3/19/82 ENTRIES BELOW.]

5/6/81 Memo to Edward Kelly, Acting Dir., Office of Special Programs, HCFA, from Nancy Cummings, M.D., Associate Dir., KUBD/NIADDK, NIH. RE: reuse of dialyzers--response to Kelly's 4/9/81 memo. "[We] support in principle *** the utility of planning a meeting to discuss dialyzer reuse. However, there are two facets to the issue which you raise about development of reprocessing standards. The most important one, which could be a very controversial and volatile one, is that dialyzer reprocessing is considered by us and by practicing nephrologists to be a component of medical practice. It would be advisable that suggested guidelines be developed by a nongovernmental 'neutral' group *** The acceptance of the nephrology community would be obtained more readily if this route were followed. We cannot emphasize too strongly the importance of the government not dictating a mode of practice. ."

5/21/81 Memo to Stuart Nightingale, M.D., Acting Assoc. Commissioner for Health Affairs, FDA, from F. Villarroel, Dir., Div. of Gastroenterology-Urology and General Use Devices, Bureau of Medical Devices, FDA. RE: reuse of dialyzers. "At the April 13 meeting *** the Gastroenterology-Urology Panel Section strongly and unanimously recommended to [FDA] to request a Consensus Development Conference on reuse.***Reuse is a controversial practice *** The Panel members were aware of Congressional interest in reuse, and that the only Government effort toward resolving this issue is being terminated this year (see attachment).***Since reuse *** is *** of significant importance for the Government, physicians, and patients, I endorse the Panel recommendation . ."

6/30/81 "MULTIPLE USE OF HEMODIALYZERS" report by Manhattan Kidney Center/National Nephrology Foundation [NORMAN DEANE, M.D., PRINCIPAL AUTHOR] under contract to the National Institute of Arthritis, Diabetes and Degistive and Kidney Diseases, NIH (mandated by Congress in 1978). [NOTE: REPORT CONCLUSIONS ARE CONFUSING AND CONTRADICTORY; AND THE CONGRESSIONALLY MANDATED STUDY ON WHICH THIS REPORT WAS TO HAVE BEEN BASED WAS DEFUNDED AND NEVER COMPLETED] ". . Studies performed in this project support the conclusion that the *** experience with formaldehyde as an antimicrobial for sterilization of [dialyzers] warrants the recommendation of continuation of its use.***The recommended concentration is 2.0% formaldehyde.*** Utilization of the specified procedures with suitable process and quality control will result in a reprocessed [dialyzer] equivalent in terms of function, cleanliness and sterility to a new hollow fiber [dialyzer].***[C]linical experience does not provide information which could appropriately lead to a standardized protocol for reprocessing dialyzers with suitable quality control and process control. The technical experience *** does not provide a suitable data base for critical analysis of the parameters of importance for reprocessing of dialyzers. A definition of conditions to effect satisfactory rinsing, cleaning, sterilization and preparation for use of a reprocessed dialyzer is necessary. ." [NOTE: THE AAMI COMMITTEE DECIDED NOT TO INCLUDE RECOMMENDED PRACTICE FOR BLOOD LINES AND PATIENT INFORMED CONSENT AND FREEDOM OF CHOICE; CONSULTANT ARTHUR D. LITTLE, INC. (ADL), WAS HIGHLY CRITICAL OF THIS REPORT IN 10/9/81 LTTR BELOW; THIS REPORT WAS REISSUED IN 2/82 WITHOUT ANY OF THE CHANGES URGED BY ADL.]

7/1/81 FDA Compliance Policy Guide 7124.16, Chapter 24 - Devices. SUBJECT: Reuse of Medical Disposable Devices. [NOTE: THIS REVISION IS IDENTICAL TO THE 11/11/77 GUIDE ABOVE, BUT DELETES THE POLICY FINDING OF ADULTERATED, AND RESULTING VIOLATION OF 21 U.S.C. 331(k).] ". . The reuse of disposable devices represents a practice which could affect both the safety and effectiveness of the device. Information developed regarding this practice should be referred to the Bureau of Medical Devices for review and evaluation."

7/31/81 Memo to Carolyn Davis, Administrator, HCFA, from Edward Kelly, Acting Dir., Office of Special Programs, HCFA. RE: dialyzer reuse. "Per your recent request, information on the potential savings, incidence and safety issues of dialyzer reuse *** If reuse, as currently practiced, was extended to 100% of facilities *** the potential savings could be as high as $150 to $200 million.***Numerous risks to patient safety have been attributed both to reuse and first use of dialyzers: (1) Infection Risk; (2) Formaldehyde induced antibodies *** which can result in increased risks of transplant rejection; (3) Pyrogenic Reactions *** reports of fever and chills; (4) Decreased dialyzer performance *** most facilities which reuse report no meaningful reduction.***While more controlled, scientific studies of these safety issues are needed, it is clear *** that there is little documented evidence of a safety risk associated with dialyzer reuse.***[The NIH] has released a final report on a laboratory study of dialyzer reuse [which] provides considerable scientific data in support of reuse. ." [SEE 8/11/81 HCFA NOTE BELOW; ALSO, SEE 10/9/81 ADL LTTR BELOW.]

8/11/81 Note to Drs. Rubin and Brandt, ASH, DHHS, from Carolyn Davis, Administrator, HCFA. RE: dialyzer reuse. "The attached memorandum related to dialyzer reuse is but one of a number of initiatives I believe we need to take in order to contain the costs of ESRD . ." [SEE 7/31/81 MEMO ABOVE.]

8/25/81 Memo to Assoc. Dir. for Device Evaluation, FDA, from Ann Holt, Assoc. Dir. for Compliance, Bureau of Devices, FDA. RE: Compliance Policy Guide 7124.16. ". . This is in response to Dr. Villaroel's memo of 8/10/81 questioning the policy section of the above referenced CPG. In late 1979, this Bureau undertook a review of all outstanding CPGs as part of FDA's effort to combine its Administrative Guides with the CPGs.***[CPG 7124.16] began the sign off process unchanged from the previous wording, however, Dr. Carl Bruch (HFK-400), then acting ADDE, objected to the wording that the device would be considered to be 'adulterated' [and] Dr. Bruch proposed the present wording.***It was not until 7/1/81, however, that the revised CPG appeared in the manual. DCO does not consider the change to be *** significant."

10/7/81 Memo to William Ketterer, DHHS General Counsel, from Harvard Gregory, Contracting Officer, NIADDK, NIH. RE: Telephone Conversation Re: Nat'l Nephrology Foundation Contract [WITH SUBCONTRACTOR ARTHUR D. LITTLE INC. (ADL)]. The question was posed as to whether a final report submitted by a subcontractor [ADL] to a contractor [Nat'l Nephrology Foundation (NNF)] *** could be disclosed upon request to a third party, or simply made public by the Government in the same manner as the Contractor's final report to the Government under the terms of the contract would be disclosed or made public. Your answer to me was no; that since the subcontract final report was submitted to the contractor, the Government did not have possession of the subcontract report. Therefore the Government could not disclose or make public what it did not possess***." [NOTE: SEE 4/23/81, 5/4/81 AND 6/30/81 ENTRIES ABOVE, AND SEE 10/9/81 AND 3/19/82 ENTRIES BELOW.]

10/9/81 Lttr to Norman Deane, M.D., Nat'l Nephrology Foundation, Inc. (NNF), from John Ketteringham, V.P., Arthur D. Little, Inc. RE: Contract No. NO1-AM-9-2214. "The final report*** 'Multiple Use of Hemodialyzers,' dated June 1981, was prepared by the Manhattan Kidney Center, submitted to the NIAMKDD without benefit of review at Arthur D. Little, Inc. (ADL). The report contained data and text taken from our report to NNF, 'The In-Vitro Evaluation of Certain Issues Related to the Multiple Use of Hemodialyzers,' dated February 1981, prepared under subcontract.***[I]nterpretations and conclusions presented in the final report to NIAMKDD are those of the [NNF] and not of [ADL]. In general.***the report fails to make clear where material referenced to ADL's and other authors' work begins and ends. Also, we urge that conclusions,such as those relating to the concentration of formaldehyde used for sterilization, be substantiated *** by clinical trials, as was envisaged in the original request for proposal *** The final report omits most of the limitations which attended data and statistical statements in the ADL report *** In particular, the final report tacitly asserts that the dialyzers which NNF submitted to ADL for testing were sufficient in number and representation to permit conclusive statistical comparisons. The ADL report makes no such assertion, and in fact advises *** that 'more extensive testing be performed to substantiate' its qualified findings.***[A] number of tables presenting data or statistical conclusions in the NNF report which are attributed to the ADL report *** are not derived from the ADL report."

2/82 "MULTIPLE USE OF HEMODIALYZERS" report by Manhattan Kidney Center/National Nephrology Foundation under NIH contractwas reissued without reflecting any of the changes urged by Consultant Arthur D. Little, Inc. (ADL) in a highly critical 10/9/81 letter. [SEE 10/9/81 ADL LTTR ABOVE; ALSO, SEE 6/30/81 ENTRY ON REPORT ABOVE]

2/18/82 Memo to Secretary, DHHS, from James Donovan, M.D., Chairman, ESRD Strategic Work Group (organized by HCFA and included managers from DHHS, HCFA and NIH--22 members in all). RE: "Chairman's Report--INFORMATION". ". . [I]ssues identified were prioritized by the Work Group***[There are] four areas of critical importance***: [1] improve [HCFA's] ESRD data base in order to provide a sound foundation for policy development; [2] ESRD prevention programs; [3] research and evaluation programs for reducing the incikdence of ESRD; [4] transplantation, reuse and rehabilitation, [including] a major clinical trial to determine effects of hemodialyzer reuse."*** Background. In 1972 Congress passed PL 92-603 which first authorized funding for the [ESRD] program. In the enacting statute, as well as in subsequent legislation (PL 95-292, 1978), Congress articulated the mission of the ESRD program: to assure patient access to high quality, cost effective medical care.***" [NOTE: THIS MEMO NEVER REACHED THE SECRETARY -- SEE 12/14/82 MEMO BELOW, AND SEE 10/5/83 ENTRY BELOW FOR MEMO AND REPORT TO ASST. SECRETARY FOR HEALTH.]

3/15/82 Lttr to Robert Wineman, M.D., NIH, from John Ketteringham, V. P., Arthur D. Little Inc. RE: "amended version" of the report, "Multiple Use of Hemodialyzers". "I read in the *** 'Gray Sheet' of March 8, 1982 *** that 'an amended version' of the report, 'Multiple Use of Hemodialyzers,' was released at a 'Dialyzer Re-Use Workshop,' on March 1, 1982. As you know, this report contains substantial pieces of work conducted at Arthur D. Little, Inc., and we would appreciate receiving a copy. Does this version address the various comments and corrections made by Arthur D. Little, Inc., to you in our letter of October 9, 1981? Or is our letter to be made available to those persons receiving this report? I note that the 'Gray Sheet' records that 2% formaldehyde is 'recommended' by this report. Our opinion is that the scientific data contained in the original version of the report did not support a recommendation, but merely showed that in specific in vitro conditions, 2% formaldehyde achieved a high kill of certain representatives pathogens. We recommend further data be generated before any recommendation is made regarding clinical practice." [NOTE: SEE JUNE 1981 ENTRY ABOVE; ALSO SEE 10/9/81 ENTRY ABOVE.]

3/19/82	Lttr to John Ketteringham, V.P. Arthur D. Little Inc. (ADL), from Robt. Wineman, Ph.D., Program Director, Chronic Renal Disease Program, NIADDKD, NIH. RE: response to Ketteringham's letter of 3/15/82 [SEE ENTRY ABOVE]. "[A] copy of the amended report "Multiple Use of Hemodialyzers" is enclosed. The revision was prepared by Dr. Deane taking into consideration the comments and corrections noted in your letter of October 9 [1981] to Dr. Deane. We have no plans to distribute the [10/9/81 letter of Arthur D. Little, Inc. with the report***." [NOTE: SEE 10/9/81, 10/7/81, 6/30/81, 5/4/81 & 4/23/81 ENTRIES ABOVE.]
APR. 1982	"Between April and November 1982, 27 of 140 patients in a [dialysis] center in Louisiana were infected with rapidly growing mycobacteria.***Of 26 identified isolates, 25 were **Mycobacterium chelonei** ssp. abscessus, and one was an **M. chelonei**-like organism. One factor common to all patients was exposure to processed [dialyzers]. Environmental sampling of the water treatment system showed widespread contamination with nontuberculous mycobacteria *** We hypothesize that patients became infected when their blood circulated through processed dialyzers that contained viable rapidly growing mycobacteria. This outbreak demonstrates that hemodialysis patients may be at risk for developing infections *** that *** may go unrecognized when routine culture methods are used. It also emphasizes the importance of using effective procedures to disinfect dialyzers in [dialysis] centers.*** The processing procedure***included rinsing the dialyzer with water, rinsing and filling with 2% aqueous formaldehyde, storing for 48 hrs, and then rinsing with sterile saline.*** Between June 1982 and June 1983, 14 (51%) of 27 patients with multiple underlying medical problems died***." [NOTE: THE DEATH OF ELAINE SHUMAN IN SEPT. 1983 IS NOT INCLUDED IN THE GROUP OF 14 PATIENTS ABOVE; SEE 6/24/85 CDC REPORT, "INFECTIONS WITH MYCOBACTERIUM CHELONEI IN PATIENTS RECEIVING DIALYSIS AND USING PROCESSED HEMODIALYZERS," PUBLISHED IN NOVEMBER 1985 IN THE JOURNAL OF INFECTIOUS DISEASES, VOL. 152, NO. 5; ALSO, SEE NOVEMBER 1985 ENTRY BELOW.]
7/29/82	Lttr "To Whom It May Concern" (at FDA) from Robt. Rosen, dialysis patient. RE: use of formaldehyde in dialyzer reuse. (GET FROM ROSEN)
9/20/82	Lttr to "Mr. Reynolds" (FDA?) from Robt. Rosen, dialysis patient. (GET FROM ROSEN)
9/21/82	Lttr to Robt. Rosen, dialysis patient, from John Newmann, President, (NAPHT) Nat'l Assoc. of Patients on Dialysis and Transplantation, Inc. Congratulates Rosen "for standing up for your right to informed consent concerning reuse. . NAPHT has been opposed to re-use. ." (and still is?).
10/2?/82	Lttr to Robt Rosen, dialysis patient, from F. Villarroel, Ph.D, Dir., Division of Gastroenterology-Urology and

General Use Devices, Office of Medical Devices, CDRH, FDA. RE: formaldehyde in dialyzer reuse. "[Y]our doctors have informed you that***you may be getting a [trace amount] of 5 ppm of formaldehyde solution at each dialysis session.*** Most individuals are chronically exposed to formaldehyde, which is a natural product found in many foods and water in trace amounts. In the human body it is rapidly transformed into formic acid, which is in turn transformed into carbon dioxide and water which are normal metabolic products.***Formaldehyde is used as an ingredient in numerous products regulated by the [FDA].***The FDA is unaware of any report of adverse reactions due to the long-term use of dialyzers disinfected with formaledhyde solutions. We trust that this information will help you in making an educated decision on whether or not to allow yourself to be treated with reused dialyzers. ." [SEE FDA LTTRS OF 12/7/82, 3/15/83 & 8/1/84 BELOW.]

12/7/82 Lttr to James Rhoades, Pa. Senate, from John Villforth, Dir., Center for Devices and Radiological Health, FDA. RE: response to Rhoades' 11/1/82 lttr. "Formaldehyde has not been shown to be toxic when ingested or injected in trace amounts.***[M]inute quantities of formaldehyde are used in several vaccines *** (etc.) *** There is no clinical evidence that formaldehyde in concentrations at or below the Kidney Foundation's guideline level are harmful to dialysis patients.***Most manufacturers have chosen to label dialyzers *** 'for one-time use only'. ." [SEE FDA 10/22/82 LTTR ABOVE; ALSO, SEE 8/1/84 FDA LTTR BELOW]

12/?/82 Lttr (undated) to U.S. Rep. James Coyne, 8th Dist. Pa., from Carolyne Davis, Administrator, HCFA. RE: response to Coyne lttr to Sec. Schweiker concerning Robt. Rosen, dialysis patient. "Multiple use of hemodialyzers has been an ongoing practice *** for 20 years.***There is no Medicare policy that requires dialyzer reuse.***In response to *** Congress, [NIH] conducted a study on reuse *** and concluded that [dialyzers] can be reused if they are reprocessed in accordance with certain procedures [SEE 2/82 NIH REPORT ABOVE].***It appears from your inquiry that Mr. Rosen is unclear about [his] right to accept or refuse reused dialyzers. "

12/13/82 Memo to Dr. Brandt, ASH, DHHS, from Dr. Hayes, Commissioner, FDA. RE: FDA's involvement in reuse of dialyzer equipment. ". . The high costs [of dialysis] have prompted examinations of ways to reduce the cost, one being the multiple use of [dialyzers].***FDA is involved in their use and reuse in three ways: Mfgrs. will soon be submitting dialyzer filters labeled for multiple use; FDA has participated in and financially supported workshops for developing guidelines for reprocessing *** In 1978, Congress mandated a study of the medical appropriateness and safety of reusing [dialyzers].***However, no clinical trials to determine the effects of reuse were included in the study.***HCFA has recently convened a *** work group to address the need for clinical studies and has prepared options suggesting ways to improve the ESRD Program's management. Those options included a recommendation that FDA conduct a clinical trial to evaluate *** reuse. Although we concur in the need for an evaluation, this Agency is not staffed and equipped for clinical research. We can, however, recommend protocols for such research and review the data from clinical trials for adequacy. ."

12/14/82 MEMO to the Executive Secretary, DHHS, from Dale Sopper, Asst. Secretary for Management and Budget, DHHS. RE: Report of the Intradepartmental Work Group on ESRD [SEE 2/18/82 ENTRY ABOVE]. "I do not concur with forwarding [the ESRD work group report] to the Secretary.***[T]his paper is incomplete and fails to respond to the Secretary's request of April 1982 for an ESRD options paper.***The Secretary met with Dr. Davis [of HCFA on 4/8/82 to] review the report***[T]he Secretary asked HCFA to submit an abbreviated options paper to him by April 23***In the paper, HCFA was to define resource requirements as well as expected benefits***I am concerned that HCFA appears to have developed its recommendations in the subject issue paper without attention to their potential budgetary impact.***As requested by the Secretary on April 8, HCFA should revise the paper to include these cost estimates as well as the benefits***. [NOTE: SEE THE 2/11/83 AND 10/5/83 ENTRIES BELOW.]

12/14/82 Lttr to Robt. Rosen, dialysis patient, from U.S. Rep. James Coyne. 8th Dist., Pa. RE: HCFA response (SEE 12/13/82 ENTRY ABOVE) to Coyne lttr. "As you can see, according to [NIH], the hemodialyzers can be reused if they are reprocessed in accordance with certain procedures.***It appears that the reuse of dialyzers is still of questionable safety. ."

1/6/83 Lttr to Robt. Rosen, dialysis patient, from Larry Oday, Dir., Bureau of Program Policy, HCFA. RE: response to a Rosen lttr. [NOTE: THIS LTTR IS ALMOST IDENTICAL TO THE UNDATED CAROLYNE DAVIS LTTR TO REP. COYNE ABOVE.]

1/6/83 Lttr to Sen. Specter from Larry Oday, Dir., Bureau of Program Policy, HCFA. RE: Robt Rosen, dialysis patient. [NOTE: THIS LTTR IS IDENTICAL TO ODAY'S 1/6/83 LTTR TO ROSEN ABOVE.]

2/11/83 Memo to Agency Heads, OASH Staff Officers, from Edward Brandt, M.D., Asst. Secretary for Health, DHHS. RE: End-Stage Renal Disease. ". . A departmental task force has made several recommendations for approaching [the ESRD] problem, and the PHS has been assigned responsibility for most of them. I find them to be both reasonable and appropriate. A copy of the report is attached.***I am designating NIH as the lead Agency to provide me with [a coordinated]response. I have asked Dr. James Wyngaarden to establish a Coordinating Committee to oversee this effort.***[I am assigning] Recommendation #4 [concerning] Dialyzer Reuse [to] FDA***." [NOTE: SEE 12/14/82 AND 2/18/82 ENTRIES ABOVE, AND 10/5/83 ENTRY BELOW.]

3/15/83 Lttr to Sen. Specter from Robt. Wetherell, Assoc. Commissioner, FDA. RE: response to Specter's 2/18/83 lttr concerning Robt. Rosen, dialysis patient. [NOTE: THIS LTTR IS ALMOST IDENTICAL TO 12/7/82 FDA LTTR TO PA. STATE SENATOR RHOADES.] "Most manufacturers have chosen to label dialyzers in the U.S. 'for one time use only'. ." [SEE FDA 8/1/84 LTTR BELOW.]

5/11/83 42 CFR Part 405. "Medicare Program; End-Stage Renal Disease Program; Prospective Reimbursement for Dialysis Services and Approval of Special Purpose Renal Dialysis Facilities; Final Rule", HCFA, DHHS, Fed. Reg. p. 21272, Vol. 48, No. 92. HCFA publishes final regulations on Medicare ESRD reimbursement rates and declares that HCFA is neutral on reuse of dialysis devices. "Reuse is prevalent in Europe and many facilities in the United States reuse. Preliminary studies show that reuse is successful where it is done properly. Nevertheless, we do not presently require or prohibit reuse. We will continue to study dializer reuse, and to monitor outcomes of those facilities that reuse dializers***to determine *** should we revise the program's health and safety, as well as reimbursement, requirements. ***The regulations establish a prospective reimbursement rate for in-facility and home dialysis of $127 per treatment. The hospitial dialysis rate is set at $132 per treatment.

7/6/83 Memo to Asst. Dir., Education and Communication, CDRH, FDA, from Mark Barnett, Dir., CDRH, FDA. RE: Meeting of CDRH working group on dialiyzer reuse, July 1, 1983. ". . Working group agreed to the following points.***It is granted that we do not have a definitive answer to the question of long term risk from dializer reuse, on the other hand there may be risk[s] from single use, which are also unknown. Given the fact of ever increasing reuse, and the encouraging lack of evidence of short term ill effects from studies to date, we should proceed to investigate the need for and possibly develop guidelines on reuse procedures.***The need for guidelines is presumptive: we do not have evidence that poor reuse practices are necessarily occurring, or that the reuse practices of some institutions are inadequate.***Guidelines will***provide assurance to patients and organized patient groups that the gov't has studied the matter and has endorsed certain principles and/or procedures as adequate. Note too, that patient [groups] as well as key medical organizations must play an active role in developing/endorsing the guidelines. The best way to develop the guidance will be through a joint NIH-FDA Consenus Development Conference. This vehicle will ***assure***participation of the right groups.***Conferees should deal***also with important issues of long term risk (do we know enough to develop guidelines?), the need for the guidance, and the question of which patients *** should not reuse. ." [NOTE: MEMO REQUESTED FROM FDA]

7/14/83 Lttr to Robt. Rosen, dialysis patient, from Mark Kramer, M.D., President, ESRD Network No. 24 Coordinating Council, Inc., King of Prussia, Pa. RE: response to 8/8/83 Rosen lttr. ". . When a dialyzer is properly sterilized its reuse is considered safe and medically acceptable. ."

8/23/83 Lttr to Robt. Rosen, dialysis patient, from J.D. Sconce, Region VI, HCFA. RE: Rosen's questions concerning deaths of 13 dialysis patients in Baton Rouge, Louisiana.

8/30/83 Minutes of meeting (1st meeting), Reuse Committee, FDA, by Lawrence Kobren, Chairperson. "With rising medical costs becoming an important issue, there is a greater probability [of reuse] of medical devices *** in order to cut costs.*** [R]euse of disposable medical devices could have a major impact on the regulatory responsibilities of the CDRH [at FDA].***Topics discussed were: Does the FDA compliance policy *** need revision? *** [I]s the labeling for [dialyzers] adequate [for reuse]? *** If reuse of a device is a medical decision, does the FDA have authority to prepare guidelines for the physician? If not, who should? Should FDA *** educate users of reused devices on the proper way to clean and sterilize devices? . ."

9/15/83 Minutes of meeting, Reuse Committee, FDA, by (unsigned). "Dr. Villarroel briefed the committee on the activities of the [Program Management Staff (PMS] ESRD Coordinating Committee.***A definition for reuse of medical devices was discussed.***Dr. Villarroel will continue his activities with regard to the PMS ESRD coordinating committee."

10/3/83 Minutes of meeting, Reuse Committee, FDA, by (unsigned). ". . Dr. Villarroel *** indicated that the memo to Dr. Brandt from the PHS Committee will endorse the concept of initiating a program using HCFA data to compare the outcome of patients treated with dialyzers one time and multiple times. The memo, however, will not include any recommendation concerning guidelines for reuse. ."

10/5/83 Memo to Asst. Secretary for Health, DHHS, from Lester Salans, M.D., Director, NIADDKD, NIH, and Chairman, PHS Coordinating Committee for ESRD. RE: Report of Committee. ". . [T]his Committee was established by you on 2/11/83 to develop a coordinated response to the recommendations contained in the February 1982 Report of the Intradepartmental ESRD Strategic Work Group [SEE 2/18/82 ENTRY ABOVE]. "SUMMARY: RECOMMENDATIONS OF THE PHS ESRD COORDINATING COMMITTEE. INTRADEPARTMENTAL ESRD STRATEGIC WORK GROUP RECOMMENDATION NO. 1--That HCFA be authorized to Implement a comprehensive Departmental ESRD database: The PHS Coordinating Committee concurs***.*** III. INTRADEPARTMENTAL *** WORK GROUP RECOMMENDATION NO.3--That NIH and HCFA individually and cooperatively develope a cohesive research plan: The PHS Coordinating Committee concurs and notes that it addresses two areas: (A) basic and clinical research and (B) program research and evaluation.*** VI. INTRADEPARTMENTAL *** WORK GROUP RECOMMENDATION NO. 6--That PHS/FDA be authorized to begin clinical trials to determine the effects of hemodialyzer reuse: The PHS Coordinating Committee does not agree *** that clinical trials *** be initiated.*** [D]ialysis using reprocessed consumables is clearly a widely accepted modification of standard treatment***A remaining issue, however, is the lack of systematic data on long-term morbidity or benifit in the reuse of dialysis consumables. To address this specific need, the PHS Coordinating Committee recommends that (1) HCFA should include information on dialyzer reuse in its comprehensive *** ESRD data base***and (2) using this data base, FDA [should] initiate a study to compare the outcome of patients treated with dialyzers used once vs. multiple times. This study should be for a period of no less than five years***The PHS Coordinating Committee recognizes that--even when careful dialyzer reprocessing and preparation procedures are followed--the possibility of long-term effects, or very infrequent acute adverse effects, cannot be ruled out completely."

11/9/83 Minutes of meeting, Reuse Committee, FDA, by L. Kobren. "The Georgetown U. Conference on Hemodialysis was briefly discussed.***Dr. Villarroel requested that the Committee review a draft Memorandum of Need (MON) for guidelines in the reuse of [dialyzers].***It was suggested [that AAMI] could establish a committee to develop guidelines if FDA provided, as a result of the MON, the necessary risks and hazards data. ."

11/30/83 FDA "Dear Doctor" letter. RE: requirements for appropriate rinsing of new dialyzers to avoid severe hypersensitivity reactions with new dialyzers.

12/5/83 Minutes of AMMI Reuse Committee mtg. (1st mtg.), Washington, D.C. [Attended by Lee Bland, CDC, and L. Kobren, FDA]. "[T]he meeting was convened to initiate work on a national consensus guideline for reuse of [dialyzers]." [NOTE: REFERENCE TO AD HOC GROUP--FDA, HCFA & NIH--TO STUDY MORBIDITY/MORTALITY IN REUSE.]

1/25/84 Minutes of meeting, Reuse Committee, FDA, by (unsigned). "The Canadian letter [from Dr. Kay of the Montreal General Hospital dated 8/15/83 and] requesting FDA funding for a [dialyzer] reuse study was . . denied because the [U.S.] government does not normally fund foreign research. . The MON for developing a guideline for reuse of [dialyzers] . . is no longer needed, since [AAMI] has agreed to develop a guideline. . Mr. Villforth will present a speech on regulatory concerns [at the Georgetown U. Reuse Conference] . . Mike Miller of AAMI is meeting with CDRH staff to

	explore possible FDA financial support for the development of the guidelines. ."
3/9/84	>Lttr to Tom Scarlett, Gen. Counsel, FDA, from J.Kevin Rooney, Atty. Re: Reuse and resterilization of Hemodialysis devices. [Rooney advises that HCFA reimbursement rate reduction has initiated a practice of reuse of dializers and blood tubing sets; He warns that the cleaning and sterilization process is not uniform.] ". . Kidney Foundation Revised Standards for reuse dated 12/2/83 ***when compared to pharmaceutical industry practices are antiquated and from the stoneage. The standards allow for bloodclots in recleaned equipment. ." [NOTE: REQUEST LTTR FROM ROONEY; ALSO, SEE 4/19/84 FDA LTTR BELOW.]
3/28/84	"Notes" of AAMI Reuse Subcommittee mtg., Washington, D.C. [attended by L. Kobren]. The "Preliminary Draft" of the "AAMI Recommended Practice: Reuse of Hemodialyzers" was discussed, including whether or not reuse of "products such as blood lines" should be included or excluded. [RE: RECENT OUTBREAK OF DISEASE AT A CENTER IN LA.]--"Nontuberculous mycobacteria *** can readily survive 2% formaldehyde after 24 hrs. of exposure.***If the concentration *** is increased to 4%, none of the strains of [the bacteria] survive beyond 24 hrs.***[A] dialysis center is faced with two alternatives.***[One] could rely entirely upon aseptic techniques throughout the reprocessing procedure *** Most centers do not have the capability of undertaking such a closed-system and experienced approach. The second option would be to use 4% instead of 2% formaldehyde . ." [NOTE: THE 6/30/81 NIH-SPONSORED REPORT RECOMMENDED 2%, BUT INCLUDED A REFERENCE TO CDC SUGGESTION FOR 4%.]
4/12/84	Lttr to Robert Taylor, Associate Administrator, Division of Health, Standards and Quality Region III, HCFA, from Frances Bowie, Service Facility Regulation Administration, Dept. Consumer and Regulatory Affairs, D.C. Government. RE: referral to HCFA of complaint received by Bowie. ". . Mr. Bland [of CDC] stated that CDC does not have a reuse blood line policy, but recommends that hospital guidelines for central service department would be appropriate in reuse processing areas.***We need to know HCFA's policy on re-using blood lines *** [W]e will need written guidelines on how to monitor its use. ." [SEE LTTR OF 7/3/84, 10/3/85 and 11/18/85 below]
4/12/84	Minutes of meeting, Reuse Committee, FDA, by L. Kobren. "[C]onsensus of the committee [on the GTU Reuse Conference was] that few if any real problems with reuse were defined. ***Some persons [at the conference] who reuse *** stated that it would be helpful if the manufacturers would provide guidance in the labeling [concerning] use of certain cleaning materials, sterilization procedures, or high level disinfection procedures.***[A draft] letter *** prepared for Mr. Villforth's signature *** requests [General

Counsel] opinion and interpretation of 21 CFR 801.4 which requires manufacturers who are aware that their device is being used for purposes other than for which it was intended to address that use in their labeling.***The 1981 ***compliance policy regarding reuse was discussed. More pressures are being exerted for reuse *** [T]he 1981 compliance policy on reuse] policy should be reexamined in light of these new pressures and we should consider whether revision or modification of our policy is necessary. The Committee decided it might be helpful to develop a Center Guideline on the various issues of reuse, such as sterility, disinfection, cleaning, and materials."

4/19/84 >Lttr to J. Kevin Rooney, Atty., from Walter Gundaker, Dir. Office of Compliance, CDRH, FDA. Re: response to Rooney's 3/9/84 lttr concerning reuse. "Hospitals that utilize raw material in the mfgr. of drugs are regulated by FDA as drug mnfgrs. and are required to register as such. This is not the case with hospitals involved with the use of hemodialysis devices which are recleaned and reused. In the case of reuse of dializers a patient-doctor relationship exist. If the doctor orders the reuse of a dializer on his patients, we have considered this to be in the realm of the practice of medicine, which is controlled by other governmental bodies, more specifically, state authorities. ." [SEE 3/9/84 ROONEY LTTR ABOVE; ALSO, NOTE: MOST STATES DO NOT HAVE LICENSURE AUTHORITY OVER DIALYSIS FACILITIES.]

4/20/84 Lttr to R. E. Easterling, M.D., chairman, AAMI Reuse Subcommittee, from M. S. Favero, Ph.D., CDC. RE: rationale for justification of using 4% formaldehyde. "Obviously, much of [your] concern [about using 4%] deals with the increased rinsing time required to remove residual formaldehyde. . CDC has never felt comfortable with the use of 2% formaldehyde *** [W]e are in the midst of a study *** of 150 *** dialysis centers *** [W]e have completed assays on 39 such centers and have detected mycobacteria in water in 35 of them. Consequently, I think the problem of mycobacterial contamination is much more widespread than we ever anticipated."

5/4/84 Minutes of AAMI Reuse Subcommittee mtg., Washington, D.C. [attended by M. Favero, CDC, & L. Kobren & F. Villarroel of FDA] "[T]he subcommittee agreed to delete *** the recommended practice dealing with informed consent.***[A] CDC survey in progress showed that *** mycobacterial contamination is far more common than previously thought." [NOTE: SEE 4/20/84 CDC LTTR ABOVE.]

/10/84 Minutes of meeting, Reuse Committee, FDA, by (unsigned). "[A] memorandum from Mr. Villforth to General Counsel request[s] a legal opinion on the applicability of [21 CFR] 801.4 *** Office of Standards and Regulations is requested to review [21 CFR] 801.4 and the draft reuse policy and give a legal opinion of both.***Review of AAMI Guideline for Reuse . ."

7/3/84	Memo to Patricia Harfst, Dir., Div. of Institutional and Ambulatory Services, HCFA, from Claudette Campbell, Acting Chief, Survey and Certification Review Branch, Region III Office, HCFA. RE: complaints from D.C. state survey agency concerning reuse of blood lines in a dialysis center. "CDC does not have a reuse blood line policy *** We feel that the health and safety issues involving reuse of the dialyzer are similar in this situation. There should be a national policy disposition regarding the reuse of blood tubing in order to ensure the protection of the health and safety of patients.*** We expect that the above will become a national concern . ." [SEE 11/18/85 HCFA LTTR BELOW.]
7/3/84	Memo to General Counsel, FDA, from John Villforth, Dir., CDRH, FDA. RE: Request for Legal Opinion of the Applicability of Section 21 CFR 801.4 [to reuse of devices]. [NOTE: A COPY WAS REQUESTED FROM KOBREN ON 1/10/86; ALSO, SEE 9/25/84 OGC OPINION BELOW.]
7/18/84	>Regulations, Colorado Department of Health: Single Use Disposable Medical Devices. RE: Reuse of dializers. "The regulations are proposed to control the re-use of single-use or disposable medical devices. Without such regulations, the public health [and] safety may be jeopardized.***Prior to individual dialyzer regeneration, each patient shall be provided by the physician with a presentation of possible complications and hazards and possible benefits of such regeneration. This shall be incorporated into the consent for dialysis form *** No person shall be denied access to dialysis in the facility as a result of the patient's refusal to permit regeneration of his or her dialyzer. Water used to formulate cleaning solution and to rinse dialyzers shall be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter.***If formaldehyde is used as the disinfecting agent, a minimum concentration of 2% in both the blood and dialysate compartments, and minimum exposure time of 24 hours if required."
8/1/84	Lttr to Robt. Rosen, dialysis patient, from John Villforth, Dir., Center for Devices and Radiological Health, FDA. RE: response to Rosen's 5/31/84 lttr addressed to President Reagan and concerning reuse of dialyzers. ". . [D]ata*** supports the safety and efficacy of the reuse of dialyzers. ***We agree, however, that the safety and efficacy of reuse is still a subject of some discussion.***[T]here are some reports in the literature regarding potential adverse affects of reuse *** FDA regulates the manufacturer and/or distributor of the device. We do not regulate the user.*** Our policy *** is to place the responsibility for reuse on the user *** [T]he Center has initiated programs which will develop data on [dialyzer] equipment, including the reuse of dialyzers.***CDRH is represented on the [AAMI] committee which is developing guidelines for the reuse of [dialyzers]." [SEE FDA LTTRS OF 10/22/82, 12/7/82 &

3/15/83 ABOVE; ALSO SEE FDA'S 9/10/84 & 9/12/84 LTTR BELOW.]

8/6/84 Lttr to FDA from Robt. Rosen, dialysis patient [GET COPY FROM ROSEN; SEE 9/12/84 FDA LTTR BELOW.]

8/10/84 Memo to Director, Office of Survey and Certification, HSQB, HCFA, from Robt. Streimer, Dir., Office of Coverage Policy, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: Policy Guidance Regarding the Reuse of Disposables for Renal Dialysis (Your memo of 7/17/84). "In your memo you mentioned a need for interim policy guidelines to address recent complaints about reuse of *** dialyzers and blood line tube sets.***[We] have no evidence of specific cases where reuse caused medical problems.***[R]esults of [the AAMI study] are expected to be released in January 1985.*** We believe it is premature to consider any change in the regulations, as you suggest, until the results of the [AAMI] project are evaluated. ."

8/17/84 Lttr to Robt. Rosen, dialysis patient, from Don Nicholson, Asst. I.G., DHHS. RE: response to Rosen's 5/31/84 lttr on reuse of dialyzers. "My office is charged with assuring the integrity of the Medicare program against possible fraud and abuse violations. However, the issue of dialyzer reuse falls specifically within the purview of [HCFA].***I feel confident that all of your concerns will be fully addressed by HCFA." [SEE 1/15/81 DHHS OIG MEMO ABOVE.]

8/20/84 Lttr to Perry Ecksel, Kidney Patient's Association, Philadelphia, Pa., from Senator Kennedy. RE: response to Ecksel concerning reuse. "FDA . . has received numerous letters of concern about the issue of reuse of kidney dialyzers. The policy of reuse of [these] devices is not directly regulated by the FDA. . If you are aware of specific instances of billing Medicare for new devices when in fact re-use of disposable items has instead taken place, you should report these instances immediately to [the DHHS OIG]. ."

8/22/84 Minutes of AAMI Reuse Subcommittee mtg., Chicago, Ill. [attended by L. Bland, CDC, & F. Villarroel, FDA] "The committee decided to exclude reuse of blood tubing from the recommended practice.***An unexplained elevation of the serum creatinine should be cause for reevaluation of the reprocessing procedure."

8/27/84 Lttr to Perry Ecksel, Kidney Patients Assoc., Philadelphia, Pa., from Henry Desmarais, M.D., Dir., Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's inquiry on reuse of dialyzers. "[R]esults of a study *** conducted by [AAMI] are expected to be released by January 1985.***While there have been reports of isolated problems with dialyzer reuse during the past few years, the documentation does not support a finding that reuse is detrimental to patient health and safety.***We can understand that ESRD facilities may wish to encourage *** reuse *** as a cost containment measure, but there is no provision in the law permitting treatment to be stopped if patients will not cooperate."

9/4/84 >Memo of Meeting to L. Kobren file, DCRH, FDA. RE: Summary notes of meeting between Kobren, Chair FDA Reuse Committee and Villforth, Dir. CDRH, FDA. RE: Robt. Rosen, dialysis patient, lttrs concerning dialyzer reuse. "[Kobren]*** described to Villforth the various points Mr.Rosen has made in his various lttrs and discussed our [FDA] responses. [MR. VILLFORTH AGREED THAT ANY FUTURE CORRESPONDENCE RELATED TO REUSE OF DEVICES SHOULD BE REFERRED TO THE CHAIRMAN OF THE REUSE COMMITTEE.]

9/10/84 Lttr to Sen. Specter from Robt. Wetherell, Assoc. Commissioner, FDA. RE: response to Sen. Specter 7/18/84 request concerning Robt. Rosen, dialysis patient. ". . Our latest letter to [Rosen] dated August 1, 1984 was in response to a letter he wrote to President Reagan on May 31, 1984.***I believe our response to his letters fully explains FDA's position with regard to the issues he has raised.***[A]s we have explained to him, many of his concerns are beyond the regulatory authority of FDA." [SEE 9/12/84 FDA LTTR BELOW.]

9/12/84 Lttr to Robt. Rosen, dialysis patient, from John Villforth, Dir., Center for Devices and Radiological Health, FDA. RE: response to Rosen's 8/6/84 lttr. ". . [Y]our concerns about the reuse of [dialyzers] *** are matters outside the jurisdiction of the FDA and must be worked out between the patient and his *** physician.***[T]he FDA is doing whatever it can, within its authority, to protect the public health by developing data on the reuse of these devices and working with voluntary standards committees to develop effective protocols for proper processing."

9/17/84 Lttr to Robt. Rosen, dialysis patient, from Lawrence Kobren, Chairman, Reuse Committee, CDRH, FDA. RE: response to Rosen's 7/25/84 lttr. ". . The FDA takes no position with respect to the decision to reuse a medical device. That decision is between a physician and the patient, and the FDA will not interfere with that process. ."

9/25/84 Memo to John Villforth, Dir., CDRH, FDA, from Ann Witt, OGC, FDA. RE: Reuse of Medical Devices; Adequate Directions for Use. "This memo responds to your request of July 3, 1984, for a legal opinion as to whether FDA can require mfgrs. of medical devices currently labeled 'for single use only' to provide adequate directions for reuse. For most devices, it is unlikely that FDA could sustain such a requirement, if imposed under a theory based on 21 CFR 801.4 that wide reuse of a disposable device by consumers constitutes a new 'intended use' of the device for which adequate directions are required. The courts have held that an 'intended use' could be established through consumer use only if consumers used the device for the use in question 'nearly exclusively'; moreover, certain factors suggest that the agency might not prevail in requiring directions for reuse even with a product as frequently reused as hollow fiber dialyzers. ."

9/28/84 Lttr to Perry Ecksel, Kidney Patients Association, Philadelphia, Pa., from Henry Demarais, M.D., Dir., Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's inquiries. ". . Under the law, [HCFA] is not authorized to recommend or prevent reuse of renal devices. Guidelines established by the FDA and the [AAMI] will be released *** after January 1985 and will address all of your concerns."

12/7/84 Minutes of AAMI Reuse Subcommittee mtg., Washington, D.C. [attended by L. Kobren, FDA] Sec. 9.4.1.1 of draft "Recommended Practice" was reworded to state: "[CDC] recommends a concentration of 4% [formaldehyde] *** lower concentrations or shorter contact times are appropriate if adequate disinfection can be demonstrated."

12/31/84 Lttr to Perry Ecksel, Kidney Patients Association, Philadelphia, Pa., from Edward Brandt, Jr., M.D., Asst. Secretary for Health, DHHS. RE: Response to Ecksel's 10/30/84 lttr to Secretary Heckler concerning reuse of dialyzers. "As a physician, I can assure you that your question concerning a patient's right to demand what you describe as 'a sterile treatment' in lieu of reprocessed equipment'***without the threat of reprisals' relates to the physician-patient relationship and is beyond the scope of the legal authority of the [FDA] or the [DHHS]. Prior consent, whether involving reuse *** or any other procedure, must be arrived at between the physician and the patient, and this is not an area in which FDA or HHS should properly be involved.***[P]hysicians and patients may differ *** as to whether specific consent for using reprocessed [dialyzers] is required.***[T]he majority of dialysis facilities reprocess [dialyzers], lending support to the premise that multiple use of [dialyzers] can now be considered standard medical practice.***If there are physicians who believe that they have the right to refuse treatment to patients who do not consent to reuse of dialyzers, then I would hope the matter could be resolved between patient organizations such as yours, the Nat'l Kidney Foundation *** and individual physicians or physician organizations.***FDA is working with the [AAMI] to develop a recommended practice for reuse.***[S]urely, for the majority of dialysis patients, an honest and trusting relationship with the physician providing treatment should be a guarantee of quality treatment whether reuse is practiced or not. ."

2/13/85 Memo to Reuse PMS (program mngmt. staff) and to DEPO, CDRH, FDA, from b. Kobren, OTA (Office of Training & Assistance), CDRH, FDA. RE: Reuse Policy Outline. ". . 2.

Reprocessing in a Clinical Facility: b. Device used on same patient (time period of use immaterial). FDA Policy--responsibility on user (reprocessor), (see CPG 7124.16 which has to be updated): no inspections; no GMP requirements; written protocols required; adverse reactions related to reuse or its procedures reported to FDA through MDR process; FDA may initiate educational information if required. Note: reprocessor not considered a mfgr. since no commercial activities are occurring . ." [NOTE: SEE 12/6/85 FDA WORKING PAPER ON REUSE POLICY, BY KOBREN, BELOW.]

3/5/85 Lttr to Carolyne Davis, Administrator, HCFA, from U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, Committee on Ways and Means. RE: concerns about reuse of dialyzers. ". . [M]any beneficiaries are concerned about the health implications of reusing devices that are labeled for one time use only. Many beneficiaries say they are being asked, and sometimes forced, to reuse.***The preponderence of *** evidence seems *** to indicate that reuse *** does not expose the patient to serious adverse health risks. I am concerned, however, that there are currently no generally accepted guidelines or regulations defining standards for reuse *** Please comment on the appropriateness of *** mandating an informed consent arrangement between the facility/physician and the beneficiary who is being asked to reuse. ."

3/5/85 Lttr to Frank Young, M.D., Commissioner, FDA, from U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, Committee on Ways and Means. [NOTE: THIS LTTR IS IDENTICAL TO THE 3/5/85 STARK LTTR TO HCFA ABOVE, EXCEPT FOR THE FOLLOWING:] "As a [dialyzer] is *** a medical device, is this not an area in which the [FDA] should be involved in? [W]hat role [do] you see the FDA playing in the *** reuse issue? [I]s there a need for regulations governing reuse, or at least guidelines? *** I am concerned that very little attention appears to have been given by the FDA to the practice of dialyzer reuse. ." [GET FDA RESPONSE TO THIS LETTER.]

3/14/85 Minutes of meeting, Reuse Committee, FDA, by Nancy Clements. ". . Kobren *** requested Committee input regarding the reuse policy.***[There was discussion of the upcoming] annual Georgetown U Conference on Reuse.***[There was] lengthy discussion *** on the draft outline of the Center Reuse Policy. Legal definitions of commerce (vs. profit), repair, reprocess, user manufacturer, etc. were discussed at length. Several Committee members expressed the opinion that the reuse policy should retain FDA's broad authority to inspect "manufacturers" but provide exemptions for hospitals, clinicians, and physicians."

4/8/85 Lttr. to Elizabeth Bridgman, Mngr., Technical Development, AAMI, from M. Favero, CDC. "[B]acteriologic and endotoxin quality of water for reprocessing dialyzers is one for which there is not a complete consensus among the committee members.***[T]here should be some degree of quality control on this type of water.***If one uses the AAMI bacteriologic standard *** there is no gaurantee that the organisms of greatest concern, the non-tuberculous mycobacteria, will be reduced since the current culture methods do not allow for their detection and their is no feasible quantitative standard.***There have been reports to the CDC where water *** which contained endotoxin subsequently resulted in pyrogenic reactions.***We have no idea of the frequency of this type of episode *** However, the risk appears to be real. . [I]f a choice were to be made between doing an endotoxin test versus a bacteriologic assay on water meant for reprocessing we would favor using the endotoxin test. ***In addition to the major outbreak of infections in Louisiana there have been two instances where non-tuberculous mycobacterial infections in dialysis patients reported to CDC. We continue to believe strongly that 2% formaldehyde *** is inadequate for reprocessing of a medical device *** The probability that viable microorganisms will be contained in the dialyzer as the result of using this inadequate procedure is high.***[R]esults of our survey of 115 dialysis centers *** show that over 80% of these centers had mycobacteria in water associated with the center. These organisms cannot be ignored.***How many outbreaks *** among *** patients are needed to indicate that 2% formaldehyde is an inadequate procedure . . ?

4/10/85 Lttr to U.S. Rep. Fortney Stark, Chairman, Subcommittee on Health, Committee on Ways and Means, from Carolyne Davis, Administrator, HCFA. RE: response to Stark's 3/5/85 ltr. "I am acutely aware of the controversy [over the absence of standards for reuse].***At the present time, I believe the question of reuse is a medical practice issue which, in the absence of specific guidelines from the [FDA], should be decided by the patient's physician. A recent study conducted by [AAMI] addresses [reuse].***When we receive the FDA comments [on this study], we will consider what steps, if any, should be taken by [HCFA], including the related question of physician/patient informed consent arrangements.***State surveyers *** do check to determine whether facilities have a written policy covering the number of times dialyzers can be safely used, including procedures for the cleaning, sterilizing and storage of dialyzers. HCFA does not, at present, provide specific standards to facilities, however. ."

4/24/85 Minutes of meeting, Reuse Committee, FDA, by (unsigned). ". . Kobren *** distributed copies of the first draft of the Health Span article on FDA's position on reuse. He also circulated copies of the Center's response to Congressman Stark's letter inquiring whether FDA needed additional legislation to regulate [dialysis] devices.***It was agreed to present [to the PMS] the need for a comprehensive reuse policy as the major issue and the

	revision of the compliance guides as a subsection.***Dr. Silverman stressed the need to change the word 'objectionable' in Compliance Guide 7424.12. Dr. Gordon and others recommended that the compliance guideline be neutral rather than positive or negative as presently stated. ."
4/26/85	Regional (HCFA Region VI) Health Standards and Quality Letter No. 85-13 To All State Survey Agencies and All Title XIX Single State Agencies. RE: Reuse of Single-Use and Disposable Medical Equipment in ESRD Facilities. ". . [R]euse is becoming a very common occurrence, particularly in ESRD facilities. The medical efficacy and safety of reuse is the subject of great debate and widely differing opinions.***The reuse of single-use items in itself should not be considered a deficiency unless prohibited by facility policy. The reuse of disposable devices without effective policies and procedures governing their reprocessing and reuse in an extremely serious deficiency which may represent a hazard to patient health and safety."(NOTE: this letter resulted from La. citing dialysis clinics for reuse.)
4/30/85	Minutes of AAMI Reuse Subcommittee mtg., Atlanta, Ga. [attended by L. Bland & M. Favero of CDC, and L. Kobren & F. Villarroel of FDA; also, of the 36 ballots cast on the "Recommended Practice", there were 3 negatives and 4 abstentions.] "The point was made that water meeting the limit of 200 colonies per ml could still contain significant amounts of endotoxin.***Consequently, if forced to make a choice, [Favero of CDC] would recommend LAL testing over bacterial colony counts."
5/21/85	Memo to Gordon Oxborrow, Minneapolis Center for Microbiological Investigation, FDA, from James J. Park, CDRH, FDA. RE: Request for study of formaldehyde and glutaraldehyde toxicity in the blood. "Study Objective--To provide FDA with data which will establish the fate of and adverse effects from formaldehyde and glutaraldehyde and their metabolites in blood."
7/2/85	Memo to Reuse PMS (Program Mngmt. Staff) & OTS Reuse WG (working group), CDRH, FDA, from L. Kobren, OTA-DTD, CDRH, FDA. RE: Plan of Action--Reuse Policy. ". . [T]he need for [FDA] to develop a policy on the reuse of medical devices, which we presented at the PMS 'Go-Away', has been accepted as a high priority issue by Center mngmt.***The first order of business will be to outline a plan of operation which will describe how we will develop the policy . ."
7/3/85	Lttr to Perry Ecksel, Kidney Patients Association, Philadelphia, Pa., from Robt. Wren, Dir., Office of Coverage Policy, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: response to Ecksel's recent letter about coverage and reimbursement for reprocessed***devices.

"The [FDA] is currently examining [the AAMI] study. When we receive the FDA comments, we will consider what steps, if any, should be taken by [HCFA].***Much data has been published which supports the safety and efficacy of reuse. Some of this information was released by the FDA to Mr. Robt. Rosen of your organization, in a letter dated August 1, 1984. ." [SEE FDA's 8/1/84 LTTR ABOVE.]

7/18/85 INTEROFFICE MEMORANDUM TO REUSE PMS AND OTA REUSE WG, FROM L. Kobren, Center for Devices and Radiological Health (CDRH), FDA. RE: Reuse Minutes. ". . Kobren *** informed [the Reuse Committee] that the development of a more comprehensive reuse policy was considered a high priority issue for the Center during FY-86.***Dr. Villarroel handed out a chart which concisely categorized FDA's possible regulation of reused disposable devices.***General Counsel should be consulted early in the process of developing the reuse policy . ."

8/85 AAMI (Aug. 1985 Revision) "Recommended Practice For Reuse Of Hemodialyzers (Proposed)", developed by the AAMI's Hemodialyzer Reuse Subcommittee (members include reps from the FDA, CDC, NIH & VA) "NOTE: Participation by federal agency representatives *** does not constitute endorsement by the federal government or any of its agencies.***The committee decided to exclude reuse of blood tubing from the recommended practice since a consensus *** could not be reached *** The committee wishes to make clear that this omission does not reflect a judgement of the merits of reusing the blood tubing.***[Dialyzer] reuse has risen *** from an estimated 16% of patients in 1980 to an estimated 60% of patients in 1983.***[This] increase *** may *** be attributed in part to the availability of new data to support the safety and efficacy of this procedure. The final report to [NIH] on a study [mandated by the Congress in 1978] states: 'Utilization of the specified procedures (for reuse) *** will result in a reprocessed *** [dialyzer] equivalent in terms of function, cleanliness and sterility to a new *** [dialyzer].***If formaldehyde is used, the [CDC] recommends that a concentration of 4 percent be used *** [T]he committee decided, after legal counsel, that [suggested elements of informed consent] is not appropriate for an AAMI recommended practice.***The committee also considered the question of whether there should be the right to freedom of choice [on whether a patient would reuse]. Consensus could not be reached on this issue due to the conflict between individual determination and cost constraints imposed by society. ." [NOTE: THE NIH REPORT CITED ABOVE WAS BASED ON AN UNFINISHED STUDY AND WAS SHARPLY CRITICIZED BY NIH CONSULTANT ARTHUR D. LITTLE, INC. IN THE 10/9/81 ENTRY ABOVE; ALSO, WHILE THE AAMI RECOMMENDED PRACTICE RECOMMENDS A 4% FORMALDEHYDE CONCENTRATION, THE NIH STUDY REPORT RECOMMENDED 2 %.]

8/8/85 INTEROFFICE MEMORANDUM TO REUSE PMS & OTA REUSE WG, FROM L. Kobren, CDRH, FDA. RE: Reuse

Committee minutes. ". . Kobren presented OTA's(?) planning schedule for development of the reuse policy.***On September 4, Mr. Arcarese and Larry [Kobren] will brief Mark Heller, [General Counsel], on the reuse policy. Dr. Andersen, [Office of Standards and Regulation], will also be [at] the meeting *** There was considerable discussion about whether or not the center had enough data on reuse to develop a reuse policy. It was concluded that the policy should be developed without detailed information on specific device reuse. ."

10/3/85 Lttr to Robert Taylor, Associate Regional Administrator, Div. of Health Standards and Quality, Region III, HCFA, from Frances Bowie, Service Facility Regulation Administration, Department of Consumer and Regulatory Affairs, D.C. Government. RE: the need for clear guidelines from HCFA on reuse. ". . the district does not have any licensure regulations for dialysis facilities or for reuse, and the federal ESRD regulations do not have clear guidelines on reuse, we are unable to enforce or persuade the facility to follow the standards of practice on reuse established by AAMI or the Kidney Foundation. Per the district's letter of Sept. 12, 1984 once again clear direction from Region III is requested on the position of HCFA on reuse. [SEE 4/12/84 AND 7/3/84 ABOVE AND 11/18/85 BELOW]

10/25/85 Speech by John Villforth, Dir., CDRH, FDA, at the Georgetown U. annual conference on reuse of disposable medical devices. RE: Reuse Of Disposable Medical Devices: Regulatory Considerations. ". . Recently *** the pressure to reduce costs by reusing disposable devices has been growing. Our concern is that as more devices are reprocessed by people with less experience in reprocessing techniques, the possibility of adverse effects to the patient increases. For these reasons FDA is developing a more comprehensive reuse policy. We also intend to examine our compliance policy guides *** Does simply labeling a device for 'single use' or 'disposable' automatically make it unfit for reuse? *** What labeling should be required with a reprocessed device? *** Should references to acceptable voluntary standards for reprocessing be included in the labeling? These and many other complex issues have to be discussed within the agency *** before any policy can be developed.***AAMI's Recommended Practice for the Reuse of Hemodialyzers *** could result in less FDA regulation.***The [JCAH] could review a facility's reprocessing procedures to determine compliance with these minimum voluntary standards.***FDA is neither for nor against *** reusing disposable medical devices. We are for the safe and effective use of medical devices . ."

NOV. 1985 "The Journal Of Infectious Diseases", Vol. 152, No. 5, included the CDC report of 6/24/85, "Infections with Mycobacterium chelonei in Patients Receiving Dialysis and Using Processed Hemodialyzers". ". . Between June 1982 and

June 1983, 14 (51%) of 27 patients with multiple underlying medical problems died***."[NOTE: THE 14 PATIENTS DO NOT INCLUDE DIALYSIS PATIENT ELAINE SHUMAN WHO DIED IN SEPT. 1983; ALSO, SEE APRIL 1982 ENTRY ABOVE.]

11/5/85 "Hemodialyzer Reuse: Issues & Solutions" (based on proceedings of an AAMI technology assessment conference in L.A. on 11/5 & 6/85). "[R]euse of [dialyzers] is likely to remain a common practice and, therefore, additional systematic studies of morbidity and mortality associated with reuse compared to single use are warranted.***[S]everal of the nonformaldehyde sterilant/disinfectants appear to have satisfactory performance for the disinfection/sterilization of reprocessed [dialyzers]." (Note: the following are statements are by Murray Klavens of NAPHT) "Informed concent is a meaningless expression unless the patient has the ability, with knowledge, to refuse, with impunity, to sign. Instead of talking about whether or not we need informed consent, we should concentrate on how to implement it so that the patient will not feel threatened. . What is needed . . are data covering large groups and generated by clinical studies." (Note: the following are statements by L. Kobren of FDA) "The FDA is *** reviewing its policy on *** reuse of medical devices.***[U]nder study is the labeling authority under part 801.4 of 21 [USE] entitled 'The meaning of intended uses'. [It] states, in effect, that a manufacturer who knows that his device is being used for conditions, purposes, or uses other than those for which it is offered must provide adequate labeling for the device to accommodate those other uses.***We recently received an opinion from the FDA's General Counsel *** which indicates that the agency may not have the authority to use the provisions of this regulation to require manufacturers to relabel their devices for reuse.***The lack of written guidance from the FDA, however, does not mean that the agency will not exercise its authority if it believes it is necessary in order to protect the public health.***We have formed a committee on reuse *** which has been directed to explore all aspects of the reuse question and to recommend, if called for, changes in policy or other actions that the [FDA] can undertake.***We see the role of the FDA as one of providing support, both technical and financial, to the professional community for the development of guidelines for reuse . ."

11/18/85 Lttr to Frances Bowie, Service Facility Regulation Administration, Department of Consumer and Regulatory Affairs, D. C. Government, from Claudette Campbell, chief, Survey and Certification Review Branch, Region III Office, HCFA. RE: response to Bowie's 10/3/85 lttr concerning HCFA position on reuse of dialyzers and bloodlines. ". . There is no official policy with respect to reuse in ESRD facilities participating in the Medicare program at this time.***[T]he draft results of a study by [AAMI] regarding reuse practices has been published and is now in circulation for public comment.***HCFA regulations, policy issuances, etc. will not be amended or changed until all results are finalized. ESRD program modifications will be forthcoming sometime in 1986 based on the AAMI effort. ." [SEE 7/3/84 HCFA MEMO ABOVE.]

11/19/85 Lttr to Pa. Governor Thornburgh from Perry Ecksel, Nat'l Kidney Patients Assn., Feasterville, Pa. RE: Re-use of Medical Disposables. ". . [W]e are now caught up in a political game.***The entire issue of re-use has gone totally out of control. In an attempt to further the financial goals of the large corporations and/or physicians, a vast network of medical abuse has erupted. ." (Obtain status from Bob Rosen: 215-752-5718)

12/3/85 Lttr to Perry Ecksel (see 11/19/85 above) from Wm. Pfaff, M.D., Nat'l Forum of ESRD networks, Inc. ". . [T]here is no practical way in which the Network Forum can adjudicate a dispute between dialysis patients and a given dialysis unit in Philadelphia. . [In my opinion] re-use is, with appropriate safeguards, appropriate and for all concerned***"

12/4/85 Lttr to Perry Ecksel (see 11/19/85 above) from Robt. Streimer, Acting Director, Bureau of Eligibility, Reimbursement and Coverage, HCFA. RE: lttrs to Secretary HHS on reuse. "While the general question of reuse is a medical practice issue and one which should be decided by the patient's physician, much data has been published which supports the safety and efficacy of reuse.***The FDA is currently examining [the AAMI's Proposed Recommended Practice]. When we receive the FDA comments, we will consider what steps, if any, should be taken by HCFA. ."

12/4/85 Lttr to AAMI from John Villforth, FDA. RE: FDA representatives for participation in AAMI's standards development committees. ". . All [FDA] nominees may be considered as voting representatives and their written ballots will reflect the views of the Center for Devices and Radiological Health. The policy of the [FDA], however, stipulates that participation by these representatives shall not necessarily reflect the agreement of the [FDA] with, nor endorsement of, any decision reached by the committee. ."

12/6/85 "Draft Working Paper; Reuse Policy Considerations", to Dir., Office of Training and Assistance, CDRH, FDA, from L. Kobren, Chairperson, Reuse Committee, CDRH, FDA. ". . Although P.L. 94-295, the Medical Devices Amendments of 1976, makes no mention of the [FDA's] specific authoriity with respect to reuse of disposable medical devices, the committee believes that FDA has the authority under the existing law to control reuse whether it is practiced by manufacturers or health professionals (including physicians, hospitals, clinics) or patients.***The reuse of disposable medical devices is a very controversial practice which raises many legal, ethical, economic, technical and safety questions.***The reuse committee believes that FDA should take a position which neither advocates nor discourages the practice of reuse, because it believes that the responsibility *** rests with the reprocessor . . Proposed Policy: (1) The reprocessing and subsequent reuse of previously used *** devices should not be considered a "new intended use" [and] therefore the reprocessor should not be required to submit a 510(k) or PMA to FDA; (2) A properly reprocessed *** device should be considered substantially equivalent to the original device; (3) Manufacturers that intend to market devices that they consider to be 'disposable' or 'single use', should substantiate that claim with FDA prior to marketing the device in accordance with existing regulations; (4) Manufacturers that do not authenticate the terms 'disposable' or 'single use', should remove those terms from the label and provide the user with information concerning the material properties of the device; (5) Medical devices that have been authenticated as 'single use' or 'disposable' should not be reprocessed; (6) Persons or facilities reprocessing previously used devices who intend to use the reprocessed device in the same facility, which [device] is not offered for sale or distributed to other facilities or persons, and which [device] is determined to be reprocessed in a manner which is generally recognized capable of producing a device which is as safe and effective as the original device should, in accordance with section 510(g)(4) of the Act, be exempt from any regulatory controls. As long as no adverse effects are associated with the reprocessing, we suggest that FDA consider these devices to be safe and the reprocessing protocols effective. However, a facility that does not have effective reprocessing protocols and/or is consistently shown to reprocess a device which causes injury to the patient, as evidenced by substantiated reports to FDA, should be treated as if it was a mfgr. ." [NOTE: ON 1/10/86, KOBREN STATED THAT FDA WAS NOW CONSIDERING TREATING FACILITIES AND PHYSICIANS AS MFGRS. AFTER ALL.]

2/24/86 "Working Paper: Policy Considerations For The Reprocessing Of Devices", by the Reuse Committee, Center for Devices and Radiological Health, FDA. "*** [T]he [reuse] committee believes that FDA has the authority under the existing law to regulate processing of devices for reuse whether it is carried out by the original manufacturers, health professionals or others. *** Federal regulation 21 CFR 820.3(k) defines a manufacturer as 'any person, including any repacker and/or relabeler, who manufactures, fabricates, assembles or processes a finished device'***. Accordingly, the Reuse Committee believes that any person who reprocesses a medical device should be considered a manufacturer. *** The Reuse Committee believes *** that all reprocessors should be required to comply with Good Manufacturing Practice (GMP) regulations (21 CFR 820) to assure that the reprocessed device continues to be safe and effective for its intended use.***"

3/6/86 The Special Committee on Aging, U.S. Senate, chaired by Senator John Heinz, conducted a public hearing on the reuse of hemodialysis devices.

6/13/86 Letter to John Heinz, Chairman, Special Committee on Aging, from Bartlett S. Fleming, Associate Administrator for Management and Support Services. RE: "*** Actions taken by *** HCFA relative to the first panel of witnesses who testified at [the] dialyzer reuse hearing. Ms. McFadden's case appears to have been resolved. *** Ms. McFadden reported that the center has a new patient Bill of Rights, that patients are being informed about BMA's grievance procedures. *** [THE] Atlanta Regional Office will investigate Mr. Vogter's case *** during the early part of June 1986. *** Malcolm Shuman, surviving son of Baton Rouge dialysis patient, Elaine Melville Shuman, did not voice any specific concerns *** which required *** HCFA investigation. *** A complaint investigation was conducted at BMA Central Philadelphia *** in response to allegations which Mr. Rosen previously shared with HCFA. *** This investigation revealed one Federal deficiency concerning the center's official policy and procedure manual not including a segment on the rules and regulations governing patient responsibilities and conduct. The deficiency was subsequently corrected. *** HCFA's policy has always been that the decision to reuse is a medical practice issue, which should be decided by a patient's physician, we do not, and will not, tolerate facilities which force their patients to reuse at the risk of being denied treatment. We will continue to monitor ESRD facilities *** and will investigate all patient complaints."

7/8/86 Memo to Asst. Secretary for Health from John E. Marshall, Ph.D, Dir., National Center for Health Science Research and Health Care Technology. Re: NCHSR Assessment on reuse and the need to take a position counter to that presented in testimony at the Aging Committee's March 6, hearing.
". . It is clear that the March 6, testimony was not based on all the germane facts. *** [There] were internal PHS documents that had not previously been shared with us. We uncovered serious omissions and inaccuracies in the testimony which had been prepared based on facts made available last March. *** Although I testified, based on information received from CDC, that they have a standard expressing the adequacy of the use of 4% formaldehyde [there] is apparently [no] formal standard and *** no CDC guidelines for disinfection. *** During testimony, we reported that HCFA and NIH [had] established a registry which would make it possible to look at issues affecting reuse. *** That information was not correct. There has not yet been a decision as to whether or not the registry will collect information on [reuse]. PHS needs to take a clinically and scientifically based stand with respect to [reuse]. We need to communicate that directly and emphatically to [HCFA], even if that means recognizing that our earlier testimony was flawed."

Item 10

HEMODIALYZER REUSE IN END-STAGE RENAL DISEASE NETWORK 7:

Assessment of current practices, revised Network 7 standards and recommendations for compliance

Report of the Hemodialyzer Reuse Task Force:

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May, 1985

Approved June 1985 for use in
ESRD Network 7
Medical Review Board
Renal Network Coordinating
Council of the Upper Midwest

Report of the End Stage Renal Disease Network 7 Hemodialyzer Reuse Survey

A survey was performed to determine the practice of hemodialyzer reuse in the 31 facilities of ESRD Network 7 one year after the National Kidney Foundation (NKF) issued "Revised Standards for Reuse of Hemodialyzers." Specific questions to be answered were:

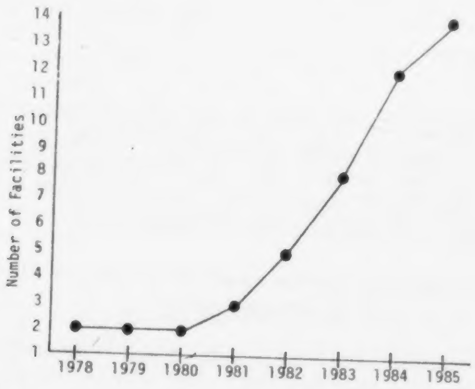
1. What is the current practice of hemodialyzer reuse in Network 7?
2. How does the practice of hemodialyzer reuse in Network 7 conform to, or vary from, the NKF Revised Standards?
3. Are the deviations from the recommended standards of a nature potentially dangerous to patients or staff?
4. What are the implications of implementing the NKF Revised Standards within Network 7?

BACKGROUND

The first standards for the practice of hemodialyzer reuse, "The Interim Standards for Reuse of Hemodialyzers" were established by the NKF in June 1982. These were adopted by the Medical Review Board of Network 7 on May 5, 1983. In December 1983, following the 1982 outbreak of a non-tuberculosis mycobacterial infection among patients in two centers which used dialyzers disinfected with formaldehyde at a central facility, the NKF issued "Revised Standards for Reuse of Hemodialyzers." The major revisions were an increase in the minimum concentration of formaldehyde from 2% to 4% in both the blood and dialysate compartments and an increase in the minimum exposure time for disinfection from 16 to 24 hours. These were in keeping with the recommendations from the Center for Disease Control (CDC) which had found this non-tuberculous mycobacterium to be resistant to formaldehyde at lower concentrations for shorter durations of exposure.

Within Network 7, the practice of hemodialyzer reuse was initiated in one facility in 1978. In 1981 a second facility began, and the practice of reuse began to increase dramatically (Figure 1). By January 1985, in the 31 facilities providing chronic care to 967 patients in Network 7, 45.2% of facilities serving 68.8% of Network 7 patients were participating in hemodialyzer reuse. By comparison, 16% of dialysis patients nationally participated in hemodialyzer reuse in 1978. By 1981, this increased to 27.5% of patients; by January 1983, 43% of the facilities and 51% of the patients in the United States were utilizing hemodialyzer reuse.

Figure 1: Number of Network 7 Dialysis Facilities Performing Dialyzer Reuse, 1978-1985



METHODOLOGY

The NKF Revised Standards (Appendix A) provided the framework for a questionnaire (Appendix B) developed to assess dialyzer reprocessing procedures in Network 7 facilities. This questionnaire was mailed to the medical directors of the facilities on January 9, 1985 to be filled out by appropriate individuals. General categories of the questionnaire included: Reuse methods and disinfectants, safety of technical staff, dialyzer individualization, dialyzer safety, esthetic appearance and criteria for discarding reused dialyzers, dialyzer effectiveness, dialyzer disinfection, consent for reuse, indications for reuse or reservations regarding reuse, and types of dialyzers being reused. The patient census of specific facilities and the current hepatitis status were provided by the Network.

FINDINGS

Questionnaires were returned by all facilities between January and April 1, 1985. Of 31 facilities reporting, 11 indicated that they do not reuse dialyzers nor do they plan to begin reuse, six are not currently reusing, but plan to begin reuse in the future, and 14 facilities are currently reusing dialyzers.

Fourteen questionnaires from reusing facilities were tabulated; nine were completed by a registered nurse in the unit, three were completed by the in vitro laboratory manager, one was completed by the unit technical supervisor, and one by the physician medical director.

The results of the questionnaire indicate that three of fourteen Network 7 units practicing reuse were unaware of any NKF standard despite its adoption by the Medical Review Board in 1983. Of the 11 units familiar with the Revised Standard, five reported compliance with the recommendations. As detailed below, no units in Network 7 are currently in compliance with all recommendations.

The findings discussed below are organized around the four basic questions of the survey. The first two questions are addressed together.

1. What is the current practice of hemodialyzer reuse in Network 7?

2. How does the practice of hemodialyzer reuse in Network 7 conform to, or vary from, the NKF Revised Standards?

REUSE METHODS AND REUSE DISINFECTANTS

All units practicing reuse employ automated systems. Eleven use a Renatron^{TM}, and two use the device manufactured by Seratronics^{TM}. One facility currently using the device manufactured by Compudial^{TM} plans to switch to a Seratronics^{TM} machine.

Five units use formaldehyde, and nine units use the Renalin^{TM} formulation of peracetic acid as the disinfectant. Two units using formaldehyde plan to switch to peracetic acid.

SAFETY OF TECHNICAL STAFF

As recommended by the NKF Standards, all units provide:

a. suitable, discreet space for reprocessing and storing used dialyzers;
b. written protocols and training for safe handling of toxic substances;
c. procedures for spills and splashes of toxic substances;
d. devices for protection from toxic substances.

Eleven of the reusing facilities control and monitor toxic fumes to meet Occupational Safety and Health Administration (OSHA) Standards. Of the three not monitoring fumes, two use peracetic acid as the disinfectant, and the third plans to switch from formaldehyde to peracetic acid.

DIALYZER INDIVIDUALIZATION

In compliance with the NKF Standards, 13 of 14 facilities label reused dialyzers with the patient's name and other unique identifying information. One labels only with the patient's name. In all units, the label is checked by two separate individuals at each use, and the number of uses is recorded both in a record maintained for the dialyzer and in the patient's dialysis record.

Thirteen of 14 facilities exclude patients with hepatitis B antigenemia from reuse in compliance with NKF Standard. Four units indicated that they had no patients who were hepatitis B antigen positive. Five units indicated on the 1984 Centers for Disease Control (CDC) Hepatitis Survey that they did treat hepatitis B antigen positive patients in 1984.

DIALYZER SAFETY

The NKF Standards prescribe that water used to formulate cleaning solutions and to rinse dialyzers should be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter (0.45 micron). Twelve of 14 facilities are in compliance with this recommendation. Eleven facilities use a reverse osmosis membrane and one facility uses deionization followed by a suitable filter. A single unit uses water which is treated by softening only, and a second uses water treated by deionization but without a 0.45 micron filter or ultrafiltration membrane.

All units report doing bacteria counts at least monthly in compliance with the NKF Standard, and 12 specified that their upper permissable limit for bacteria was less than 200 colonies per milliliter. One unit did not specify its permissable level and one unit specified that the count must be equal to or less than 250 bacterial per milliliter. Seven units indicate that their testing is done by the Millipore Total Count Sampler^{TM}.

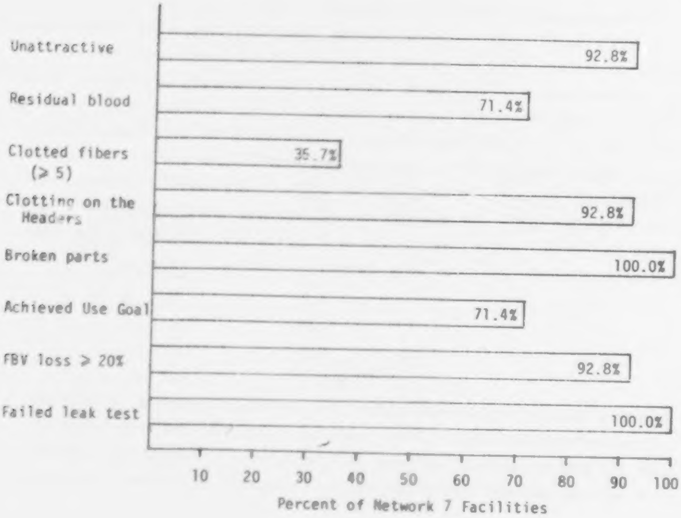
The NKF Standard requires that reuse water contain a level of bacterial endotoxin of less than 1 nanogram per milliliter which is documented by Limulus amoebocyte lysate (LAL) testing not less than monthly. Only four units indicate compliance with this recommendation. It is noteworthy that the units which did not have either an ultrafiltration membrane or a 0.45 micron filter also do not perform LAL testing.

The NKF Standard requires maintenance of a log of all febrile reactions during dialysis and a written procedure, including blood and dialysate cultures, during all febrile reactions. Ten facilities indicate that they maintain such a log with eight facilities having a written procedure which includes appropriate cultures. Thirteen facilities indicate that they maintain the recommended log for blood leaks. Twelve facilities maintain a record of patient reactions to disinfectant, however, only two facilities indicate that they have physician's orders for dealing with such reactions.

ESTHETIC APPEARANCE AND CRITERIA FOR DISCARDING REUSED DIALYZERS

All units discard dialyzers which were either broken on visual inspection or which failed a pressure test (Figure 2). Nearly all units (92.8%) discard the dialyzer if it was unattractive, had clotted headers or had a loss of fiber bundle volume equal to or greater than 20%. Most (71.4%) units discarded dialyzers which were discolored by residual blood or which had reached a predetermined number of uses. Only 35% of the facilities discarded dialyzers that had five or more visible clotted fibers after reprocessing. This criterion, however, relates only to units which use formaldehyde as a disinfectant because peracetic acid bleaches even clotted fibers white.

Figure 2: Criteria for Discarding Reused Dialyzers



DIALYZER EFFECTIVENESS

The NKF Standard recommends that "validation studies including at least *in vivo* or *in vitro* clearances of creatinine and urea and ultrafiltration rate of each dialyzer type reprocessed by a facility should be conducted not less than quarterly." Only one facility indicated compliance with this recommendation by monthly *in vivo* testing. A second facility performs *in vivo* testing every six months and a third facility indicated performance of *in vitro* testing whenever a new dialyzer or reuse procedure was initiated.

DIALYZER DISINFECTION

Of 14 facilities practicing reuse, five use formaldehyde as a disinfectant, and nine use peracetic acid as disinfectant. Of the five facilities using formaldehyde, three facilities report adding 4% to both the dialysate and blood compartments, while two indicate storage concentration in both compartments of approximately 2.5%. The manufacturer's specifications indicate that not all the machines in use in those sites are able to deliver a 4% concentration of disinfectant to both compartments. Consequently, some of the facilities which utilize formaldehyde are not in compliance with the NKF recommendations. To date, the NKF has not recommended a concentration standard for peracetic acid. The manufacturer of peracetic acid indicates that a concentration of 750 mg/l and a contact time of 11 hours will effectively disinfect reused dialyzers provided that other requirements for its application are also met.

CONSENT

The NKF Standard states that informed consent for the reuse procedure is essential and that if patients do not sign a consent form to reuse, they are entitled to a new dialyzer for each treatment. Only one unit in Network 7 reports that consent for reuse is not obtained and that participation in hemodialyzer reuse is mandatory.

REASONS FOR REUSE AND RESERVATIONS ABOUT REUSE

In describing reasons for reuse, 92.8% of units listed economic considerations, 42.8% of units indicated a reduced incidence of first-use syndrome, 37.7% of units indicated that patients feel better and 7% of the units did not respond.

The one reservation about reuse, a concern about the long-term effects of exposure to disinfectants by both patients and staff, was listed by 57% of the units. Four units (28.5%) indicated that they had no reservations, and one unit questioned whether reuse is cost effective and expressed reservations regarding the related volume of record keeping required.

TYPES OF DIALYZERS REUSED IN NETWORK 7

The types of dialyzers used, the average number of uses and the range and number of units using a particular brand of dialyzer are shown in Table 1.

Table I
Hemodialyzer Reuse Network 7 by Dialysis Type

	Number of Uses		Number of Facilities Reusing This Type
	Mean	Range	
Travenol CF 1211	7.9	4-15	12/14
Travenol CF 1511	7.7	4-12	12/14
Travenol CF 2308	7.0	6- 8	2/14
Cordis Dow 90	6.0	--	1/14
Cordis Dow 135	6.0	--	1/14
Cordis Dow 3500	6.0	4-10	3/14
Cordis Dow 4000	5.0	4- 8	5/14
TAF 10	5.8	4-12	4/14
TAF 12	8.0	6-12	3/14

3. Are the deviations from the recommended standards of a nature potentially dangerous to patients or staff?

The survey has revealed several deviations from the Revised Standard. Four (VI, VII, VIII, IX) are considered highly significant and prompt corrective action is recommended. We will discuss each deviation in terms of the purpose of the standard, potential clinical significance of noncompliance, and recommendations for action.

I. Failure to label each used dialyzer with the patient's name and other unique identifying information. Units involved: 1.

The purpose of requiring two forms of identifying data is to minimize the risk of patients with similar names receiving another individual's dialyzer. Even with two labels, dialyzer mix-up occasionally occurs. Although no adverse reactions have been reported from this, it is certainly to be avoided.

RECOMMENDATION: Compliance for all units. This is a quick, easy, inexpensive process to implement that may prevent dialyzer mix-up.

II. Failure to maintain a log of febrile reactions during dialysis and
III. Failure to maintain written protocols, including blood and dialysate cultures during febrile reactions. Units involved: 4 and 6 respectively.

The purpose of this standard is to provide an epidemiologic monitor for disinfection as a signal to reevaluate the reuse procedure if febrile reactions with reused dialyzers exceed those seen with new dialyzers.

RECOMMENDATION: Complete compliance. Logs of febrile reactions and a protocol for appropriate cultures are easily implemented in all settings.

IV. Failure to perform quarterly validation studies of dialyzer performance. Units involved: 13.

The purpose of this standard is to ensure that patients are treated with dialyzers which though reused, perform to expected specifications for diffusion and ultrafiltration. All facilities in Network 7 currently use commercial, automated reuse devices, and no facility is performing manual reuse. It is our opinion that the need for performance testing is greatly diminished with automated systems as manufacturers imply adequate performance if conditions for installation, operation and dialyzer discard are met. The need for validation testing may be further diminished if patients are carefully monitored by serum chemistries at least monthly and if variations in these chemistries are systematically evaluated. Systematic evaluation would include verification of adequate blood and dialysate flow rates as well as studies to assess access recirculation in addition to dialyzer performance. To require quarterly testing in the setting where patient chemistries are routinely monitored and documented to be stable and where appropriately maintained automated reuse procedures are followed is probably excessive.

RECOMMENDATION: Validation testing is probably unnecessary on a quarterly basis where automated systems are used unless changes in patient chemistries and/or fluid status indicate need for review of these parameters.

V. Failure to exclude patients who are hepatitis B antigen positive from hemodialyzer reuse. Units involved: 1.

The purpose of this recommendation is to minimize risk of transmitting hepatitis to dialysis staff or other antigen negative patients.

RECOMMENDATION: Complete compliance with this regulation unless:

a. All hepatitis B antigen positive patients are treated in an isolation area distinctly separate from antigen negative patients and which includes separate dialysis delivery systems.

b. Vaccination with Heptavax be recommended and provided for all antigen negative patients and staff and the efficacy of vaccination be documented by antibody testing.

c. Dialyzers from antigen positive patients be reprocessed in an area separate from that used for reprocessing dialyzers from antigen negative patients.

d. That a separate automated reuse device be used only for patients who are hepatitis B antigen positive.

Unless a facility treats a large number of antigen positive patients, it will not be cost effective to operate a separate unit and reprocessing area for these individuals. It is noteworthy that with application of routine screening tests for the hepatitis B surface antigen, the strict isolation of antigen positive patients, and the vaccination of antigen negative individuals, new cases of hepatitis B have been virtually eliminated. In 1984, only 2 new cases of hepatitis B were reported and a total of 17 antigen positive patients were treated in 28 Network 7 facilities which completed the CDC Hepatitis Survey.

By contrast, 15 new cases of non-A, non-B (NANB) hepatitis were reported by these Network 7 facilities in 1984. It seems certain that NANB hepatitis either is, or soon will be, the major hepatitis in the dialysis setting. The risk of developing NANB hepatitis after receipt of a single unit of blood has been reported to be as high as 7%. Considering that 5 to 10 units of blood are now recommended for younger patients prior to transplantation and that the number of elderly patients with organic heart disease who receive transfusions to control angina is increasing, the potential for significant numbers of patients developing NANB hepatitis is readily apparent. Since definitive diagnostic tests or uniform diagnostic criteria for NANB hepatitis are unavailable, patients suspected of having NANB hepatitis should be excluded from hemodialyzer reuse.

VI. Failure to treat water for reuse with a reverse osmosis membrane, ultrafiltration membrane or 0.45 micron filter; and

VII. Failure to document a level of bacterial endotoxin of less than 1 nanogram per milliliter monthly. Units involved: 1 and 10 respectively.

The purpose of this guideline is to control the load of bacteria presented to the dialyzer which must be eradicated by the disinfectant and to document low levels of endotoxin which may contribute to pyrogen reactions during dialysis. These standards require users to control both bacteria and pyrogen. Therefore, it is important to note that a reverse osmosis membrane or ultrafiltration membrane can remove both bacteria and pyrogen, while a 0.45 micron filter will only remove bacteria. Ultrafiltration membranes have a higher initial cost than the 0.45 micron filter, however, they are reusable for extended periods of time and have superior organic filtration characteristics. LAL testing is modest in cost and of considerable potential benefit.

RECOMMENDATION: Compliance with LAL testing.
Compliance with NKF water treatment standard with strong encouragement for the use of ultrafiltration membranes rather than the 0.45 micron filter which is also acceptable.

VIII. Failure to use 4% formaldehyde in both the blood and dialysate compartments. Units involved: 3 (and possible more, depending on the reuse device utilized)

The purpose of this recommendation is to avoid a second outbreak of nontuberculous mycobacterial infection as occurred in Louisiana. The Louisiana outbreak involved 24 patients, 13 of which died. While the extent to which the mycobacterial infection contributed to their deaths in unknown, it would be indefensible to ignore the CDC/NKF recommendation for 4% formaldehyde in light of this data.

The risks of outbreaks such as occurred in Louisiana exist whenever formaldehyde is used in concentrations of less than 4% and are increased if this is coupled with the use of inadequate water purification systems. A further liability of these circumstances is that conventional bacterial culture techniques, including the Millipore Total Count Sampler™, are incapable of detecting the atypical mycobacteria which have the potential for formaldehyde resistance. Moreover, water supplies which do not presently contain such organisms cannot be relied upon to remain so in the future.

RECOMMENDATION: Strict compliance; i.e. if formaldehyde is used, it must be added to a minimum concentration of 4% in both compartments of the dialyzer with an exposure time of 24 hours. Facilities using formaldehyde should document a 4% concentration in the dialysate and blood compartments by testing through an independent laboratory or other suitable technique at initiation of the system and every six months thereafter.

IX. Failure to monitor potentially toxic fumes to OSHA levels. Units involved: 3.

The purpose of this standard is to protect both patients and dialysis personnel from exposure to toxic levels of disinfectants.

Two disinfectants, peracetic acid and formaldehyde, are currently employed for dialyzer reuse in Network 7. An OSHA standard is available only for formaldehyde fumes. Although not covered in the survey, units may use formaldehyde for disinfecting delivery systems, water systems, etc., which would also require monitoring.

For facilities in the State of Minnesota (9/14) compliance with the Minnesota Employees Right to Know Act (MERTKA) of 1983, which also addresses issues of chemical monitoring and safety, is mandatory and not simply a recommendation.

RECOMMENDATION: Compliance with both OSHA and, where applicable, MERTKA regulations.

4. What are the implications of implementing the NKF Revised Standards for Hemodialyzer Reuse within Network 7?

Except as previously noted within this report, compliance with the NKF Interim Standard within Network 7 is relatively high. This standard, which has been endorsed by the Network Medical Review Board, has been revised by the NKF to reflect the need to increase formaldehyde concentration to 4%. In light of the findings and recommendations of the CDC, the use of formaldehyde at lower concentrations must be considered unacceptable.

In addition to the present NKF Revised Standard, similar standards have been or are being developed by other ESRD Networks, some states and the Association for the Advancement of Medical Instrumentation. The latter, which is still under development, will be more extensive than any yet seen.

Our recommendation to the Network at this time is to endorse the NKF Revised Interim Standard with the following modifications:

1. Validation studies of dialyzer performance are necessary only if changes in patient's chemistries or fluid status indicate such a need providing that
    a. properly installed and maintained automated reuse systems are employed and operated according to the manufacturer's instructions, and providing that
    b. patient fluid status and chemistries be carefully monitored (at least monthly) and documented to be stable and satisfactory.

2. Patients who are hepatitis B surface antigen positive may participate in hemodialyzer reuse if all conditions listed on p. 10-11 are met. Patients suspected of having NANB hepatitis should be excluded from hemodialyzer reuse.

3. All facilities are strongly encouraged to use reverse osmosis or ultrafiltration membranes as part of the treatment for reuse water.

4. The requirements for dialyzer reuse in the home should be separately developed as those of the NKF cannot be practically implemented.

5. The Network administration should ensure a complete flow of information concerning its reuse position to facilities' physician, nursing and technical staffs. This recommendation is made because three facilities practicing reuse in Network 7 were not aware of the NKF Standard.

6. The Network should consider providing professional and/or technical assistance to facilities either reusing or contemplating reuse.

COVER STORY

Exclusive Presentation of Important NKF Consensus Reuse Standards

NATIONAL KIDNEY FOUNDATION REVISED STANDARDS FOR REUSE OF HEMODIALYZERS

December 2, 1983

The Executive Committee of the National Kidney Foundation has decided to issue these Standards for Reuse of Hemodialyzers in the interest of better patient care.* These standards will be reviewed periodically as the science of dialyzer reuse develops. Accordingly, the Foundation requests comments and suggestions from all interested parties.

The practice of reuse of hemodialyzers, which involved 16 percent of U.S. patients in 1978, increased to 27.5 percent of U.S. patients in the fall of 1981. Recent CDC surveillance of 1,015 dialysis facilities [out of about 1,300 total] treating 65,812 patients showed that, as of December 31, 1982, 43 percent of facilities and 51 percent of patients were utilizing dialyzer reuse. It is appreciated that new dialyzers contain potentially toxic residues of the manufacturing process, and that used dialyzers contain potentially toxic residues of the reprocessing procedure. It is also recognized that appropriate procedures are capable of reducing the levels of these residues to the point that acute reactions to new and to used dialyzers are infrequent, and that chronic toxicity has not been described. It is important, however, to continue long-term studies of potential toxicity of new and used dialyzers.

Manufacturers of new dialyzers appropriately utilize a number of different techniques to produce dialyzers, but all new dialyzers must meet certain standards of safety, usually assumed by validation studies of a small sample of the product. Each dialyzer type is credited with certain standards of performance based upon manufacturing specifications and supported by periodic validation studies of small samples of the product. Similarly, a facility that reprocesses dialyzers is responsible for producing a safe and effective product (FDA Compliance Policy Guide 7124, 23, Nov. 1977). Although a number of different techniques are appropriately utilized to reprocess dialyzers, the growing practice of dialyzer reuse now makes it mandatory to develop standards of safety and performance for reprocessed dialyzers.

The patient has the right to expect—and the facility the obligation to provide—professional, safe and effective care at all times. A system, and specific written procedures, concerning all elements of dialyzer reuse should be developed by each facility practicing reuse. These aspects of reuse are appropriately individualized to the particular facility, but should be directed to achieve an effective, safe system, and a uniform product.

The system should provide suitable discrete space for reprocessing and storing used dialyzers; define and document personnel training; assure personnel safety by written protocols and training concerning safe handling of toxic substances; provide procedures for spills and splashes of toxic substances; provide devices for protection from toxic substances (goggles and masks); and provide for control and monitoring of toxic fumes to or below recognized Occupational Safety and Health Administration (OSHA) standards.**

> ***If formaldehyde is used as the disinfecting agent, a minimum concentration of four percent in both the blood and dialysate compartments, and a minimum exposure time of 24 hours is mandatory. This standard is developed in keeping with recent CDC studies.***

The product must meet minimum standards which should include individualization of dialyzers, safety in subsequent application, effectiveness during subsequent use, a suitably esthetic product, and consent.

INDIVIDUALIZATION

1. Each dialyzer to be reused must be indelibly and clearly labeled with the patient's name and other unique identifying information before or during the initial use.
2. At each subsequent use, the label should be checked by two separate individuals, usually the dialysis staff member and the patient, if feasible.
3. The number of the use should be recorded both in a reuse record maintained for each dialyzer, and in the patient's permanent dialysis record.

This standard should assure individualization of the dialyzer, permit retroactive tracking of the dialyzer in the event of dialyzer failure or reaction during use, and generate records of performance of reprocessed dialyzers suitable for program analysis.

In addition, reuse of dialyzers is not recommended in patients who are Hepatitis B antigen positive because of the potential risk of transmission of hepatitis to dialysis staff and other patients.

SAFETY

Safety of the reprocessed dialyzer is assured by the use of suitable solutions for rinsing, cleaning and disinfecting the dialyzer, and by the subsequent effective removal of these solutions.

1. Water used to formulate cleaning solution and to rinse dialyzers shall be passed through a reverse osmosis membrane, ultrafiltration membrane or a submicron filter (0.45 micron) which is appropriately maintained. This water must contain less than 200 bacteria per mL, which should be documented by bacteriologic sampling of the source water outlet in the reprocessing area at least monthly. Where such sampling reveals bacterial counts that periodically approach or exceed this limit, corrective measures and weekly sampling are indicated. Results of such samples should be appropriately recorded.
2. Water containing a level of bacterial endotoxin (pyrogen) of less than 1 mg/mL, documented by a suitably sensitive, negative limulus amoebocyte lysate (LAL) test not less than monthly, must be used to formulate the disin-

Continued on page 37

Continued from page 29

Recent U.S. Centers for Disease Control surveillance of 1,015 dialysis facilities (out of about 1,300 total) treating 65,812 patients showed that, as of December 31, 1982, 43 percent of facilities and 51 percent of patients were utilizing dialyzer reuse.

fecting solution. A sub-micronfilter, in line between the disinfectant reservoir and the disinfectant outlet is necessary to remove particulates.

3. There is little information concerning the effect of chemicals commonly found in potable water on any aspect of reprocessing, its effectiveness, or its safety. Therefore, no standard is proposed. However, the possibility of chemical absorption by the dialyzer membrane during reprocessing and unknown effects of such absorption on safety and efficacy of reuse suggest the need for further study of this question and have prompted some facilities to use water meeting AAMI chemical standards in reprocessing dialyzers.
4. Disinfection must be achieved with an effective agent, the addition of which to each dialyzer must be documented and recorded. If formaldehyde is used as the disinfecting agent, a minimum concentration of four percent in both the blood and dialysate compartments, and a minimum exposure time of 24 hours is mandatory. This standard is developed in keeping with recent CDC studies. Further investigation is required to determine if lower concentrations of formaldehyde effectively eliminate fastidious organisms found in some water sources. If any other disinfecting agent is employed, effective concentrations, contact characteristics, and exposure time must be established and utilized and shown to be equivalent to formaldehyde in effectiveness.
5. Disinfection should be monitored epidemiologically by means of a log of all febrile reactions during dialysis with new or used dialyzers, and a written procedure including dialysate and blood cultures during all febrile reactions. A febrile reaction rate greater with used than with new dialyzers requires a careful reevaluation of all elements of the disinfection process. Routine validation studies of blood compartment disinfection are not productive in the clinical setting.
6. Documentation and recording of the addition of effective disinfectant concentrations in the dialyzer to be reused is mandatory.
7. Documentation and recording of effective disinfectant removal from each dialyzer immediately prior to reapplication is mandatory. If formaldehyde is used as the disinfecting agent, a Schiff's reagent-based test, negative after five minutes, is suitable screening test for each dialyzer. Validation tests of methodologic achievement of 5 mcg/mL (5 ppm) or less should be made at least monthly.
8. Removal of any other potentially toxic substances added as any part of the reprocessing procedure should also be documented and recorded by routine testing and/or validation studies as may be appropriate.

EFFECTIVENESS

1. The effectiveness of the reprocessing procedure must be documented before each subsequent use of each dialyzer.
2. For hollow fiber dialyzers, a hollow fiber bundle volume (HFBV) of not less than 80 percent of the initial HFBV, measured at 0 ± 10 mm of Hg transmembrane pressure, is a sufficient measure of residual effective function.
3. At the present time, no satisfactory, generally acceptable test exists to measure residual function of parallel plate or coil dialyzers except small molecular clearance, which precludes multiple use of plate and coil dialyzers at this time, unless clearance tests are performed after or during each use.
4. Blood leaks during use of both new and reprocessed dialyzers should be documented and recorded. If the blood-leak rate of used dialyzers exceeds that of new dialyzers, each dialyzer must be pressure tested for possible blood compartment leak before reuse.
5. Validation studies including at least *in vivo* or *in vitro* clearances of creatinine and urea and ultrafiltration rate of each dialyzer type reprocessed by a facility should be conducted not less than quarterly.

ESTHETIC APPEARANCE

A critical visual inspection of each dialyzer is necessary to detect cracked or broken parts, and to assure a clean, pleasing appearance. It is unreasonable and inappropriate to present an esthetically unattractive dialyzer to the staff or patient for reuse.

1. Reprocessed dialyzers must appear clear, and free of dissolved or residual blood manifest by a brownish or pinkish tinge.
2. A few (five or less) visible, dark, clotted fibers are acceptable.
3. The headers should be visibly free of all but small peripheral clots.
4. Failure to meet these criteria requires that the dialyzer be discarded.

CONSENT

Ethical aspects of dialyzer reuse concern the rights of the several members of the dialysis community. All members of the community benefit from Medicare funding for End-Stage [illegible] Disease care, and all share the [illegible]ity for limiting program costs, while [illegible]ing access to quality care. The principles of informed consent are a truthful presentation of possible complications and hazards of therapy, the benefits to be expected from therapy, and the alternatives to hemodialysis therapy.

Patient informed consent for the reuse procedure as practiced by the center at which the patient dialyzes is essential. If patients do not sign a consent form to reuse, they are entitled to a new dialyzer for each hemodialysis treatment.

MISCELLANEOUS

Reuse of dialyzers by individual home patients has been safely and effectively practiced for many years. This practice should observe the same principles, and the same specific standards, elaborated for reuse in facilities. A system for reprocessing should be established and monitored by the home training facility with written procedures and training directed toward the protection of the patient and family members from injury in handling and using toxic substances. Procedures, training, and testing should be provided to assure the safety and effectiveness of reprocessed dialyzers, the same as for dialyzers reprocessed by the facility. All procedures should be reviewed semi-annually in the home setting for compliance.

These standards are intended to assure safe and effective multiple dialyzer use, but are not intended either to encourage or constrain this practice. A specific limit on the number of uses of any reprocessed dialyzer is arbitrary and inappropriate, as long as all the criteria of individuality, safety, effectiveness and appearance are met. The standards are readily achievable, represent currently available and practiced technology, and should be periodically modified by the consensus of broadly representative and expert assemblage as technology changes. ☐

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*The National Kidney Foundation convened a group with expertise and experience in dialysis, including one or more physicians, nurses, consumers (patients), industry representatives, and microbiologists to formulate these standards, which were subsequently approved by the Executive Committee of the National Kidney Foundation at its December 2, 1983 meeting.

**The standard for formaldehyde requires an 8-hour time weighted average (TWA) concentration limit of 3 ppm, a ceiling concentration of 5 ppm, and an acceptable maximum peak above the ceiling concentration of 10 ppm for no more than a total of 30 minutes during an 8-hour shift.

QUESTIONNAIRE
REUSE OF HEMODIALYZERS
ESRD NETWORK 7

FACILITY IDENTIFICATION: ____________
Name of Person Completing Questionnaire: ____________
Title of Person Completing Questionnaire: ____________

1. Are you currently using reprocessed dialyzers?

   a) Yes ____ b) No ____

   a. If No, do you plan to begin using reprocessed dialyzers?

   c) Yes ____ d) No ____

2. Please fill in the diagram below with your facility's water treatment system. Include softener (S), carbon filter (CF), reverse osmosis membrane (RO), sediment filter (SF), ultrafiltration membrane (UF), ultraviolet light (UV), 0.45 micron filter (MF), holding tank (HT), deionizer (DI), etc.

Water Source

STOP if the answer to question 1 is NO and please return the questionnaire to the Network office. Go on to Questions 3-40 if the answer to question 1 is YES.

3. How long have you been reusing dialyzers? ____________

4. Are you familiar with the National Kidney Foundation Revised Standards for Reuse of Hemodialyzers?

   a) Yes ____ b) No ____

5. Is your reprocessing procedure in compliance with these NKF Standards?

   a) Yes ____ b) No ____

6. If you use an automated system for reprocessing dialyzers, specify type: ____________

7. Which of the following does your facility provide to assure safety during the reprocessing procedure? (Check all that apply)

- ____ suitable discreet space for reprocessing and storing used dialyzers
- ____ written protocols and training for safe handling of toxic substances
- ____ procedures for spills and splashes of toxic substances
- ____ devices for protection from toxic substances
- ____ control and monitoring of toxic fumes to or below OSHA standards

8. Is each dialyzer to be reused indelibly and clearly labeled with the patient's name and other unique identifying information before or during the initial use?

a) Yes ____ b) No ____

9.* At each subsequent use, is the label checked by two separate individuals?

a) Yes ____ b) No ____

10. Do you record each use in a reuse record maintained for each dialyzer and in the patient's permanent dialysis record?

a) Yes ____ b) No ____

11. Do you reuse dialyzers in patients who are Hepatitis B antigen positive?

a) Yes ____ b) No ____

12. Is the water used to formulate cleaning solution and to rinse dialyzers treated in the system diagramed in Question #2?

a) Yes ____ b) No ____

a. If No, please diagram the treatment system for this water.

Water Source

13. How frequently do you perform bacteriologic sampling of the water used in reprocessing? ____________

14. What value do you use as a permissible bacteria level? ____________

15. Do you utilize the Millipore total count sampler for bacteriologic sampling?

a) Yes ____ b) No ____

16. Do you perform limulus lysate testing on your reuse water?

a) Yes ____ b) No ____

17. If the answer to question number 16 is yes, how frequently is this done?
Please describe ____________________

18. Indicate the types of dialyzers reused in your facility.

	1	2	3	4	5
Manufacturer					
Dialyzer Model					

19. Approximately how many uses do you achieve with each dialyzer type?

	1	2	3	4	5
Dialyzer Model					
Average Uses					

20. What criteria determines that a dialyzer should be discarded? Please check all that apply.

____ The dialyzer has failed a pressure (leak) test
____ The dialyzer fiber bundle volume has decreased by 20% or more
____ The dialyzer has reached a predetermined maximum number of uses
____ Clotting evident on the headers
____ Cracked or broken parts detected by visual inspection
____ Dissolved or residual blood manifested by a brownish or pinkish tinge
____ More than five visible, dark clotted fibers
____ An esthetically unattractive appearance
____ Other, please specify ____________________

21. Do you perform validation studies for clearance rates of urea and creatinine and of ultrafiltration coefficients for each type of dialyzer being reused?

a) No ____ b) Yes, quarterly ____
c) Yes, other interval (please specify) ____________________

22. If you perform validation studies, are they done

a) In vivo ____ b) In vitro ____ c) Both ____

23. What type of disinfectant do you use?

a) Formaldehyde ____ b) Renalin ____
c) Cidex DS ____ d) Sporicidin ____
e) Warexin ____ f) Other, specify ____

24. What is the concentration of the disinfectant added to

a) The blood compartment ____________
b) The dialysate compartment ____________

25. How frequently do you measure and record the concentration of disinfectant recovered from stored dialyzers (before rinsing).

a) Never ____ b) Each dialyzer ____
c) Other Interval, specify ____________________________

26. If you perform the measurements referred to in question number 25, what test method(s) is used?

Please describe ____________________________

27. How frequently do you measure and record the residual concentration of disinfectant in dialyzers after rinsing?

a) Never ____ b) Each dialyzer ____
c) Other Interval, specify ____________________________

28. If you perform the measurements referred to in question number 27, what test method(s) is used?

Please describe ____________________________

29. What is the maximum concentration of residual disinfectant you allow after dialyzer rinsing?

Please specify ____________________________

30. Have you performed measurements of residual disinfectant "rebound" occurring after dialyzer rinsing is completed?

a) Yes ____ b) No ____

31. Do you maintain a log of acute patient **reactions** to residual disinfectant?

a) Yes ____ b) No ____

32. Do you have a written procedure for patients experiencing acute reactions to residual disinfectant?

a) Yes ____ b) No ____

33. Do you maintain a log of febrile reactions during dialysis with new or reprocessed dialyzers?

a) Yes ____ b) No ____

34. Do you have a written procedure which specifies that dialysate and blood cultures be drawn during all febrile reactions?

a) Yes ____ b) No ____

35. Do you document the number of blood leaks during use of both new and reprocessed dialyzers?

a) Yes ____ b) No ____

36. Do you obtain patient informed consent for the reuse procedure from those patients who are using reprocessed dialyzers?

a) Yes ____ b) No ____

37. Are your patients allowed to refuse to participate in dialyzer reuse?

a) Yes ____ b) No ____

38. Please list your reasons/indications for dialyzer reuse. ____________________

____

____

39. Do you have any reservations regarding reuse concerning either patients or staff?

a) No ____ b) Yes, please describe ____________________

____

____

40. Do you follow home dialysis patients who reuse dialyzers?

a) Yes ____ b) No ____

STOP if your answer to #40 is NO. Please return the questionnaire to the Network office. Go on to answer questions 41-43 if the answer to #40 is YES.

41. Do you have written procedures and training for home patients and family members practicing reuse of dialyzers?

a) Yes ____ b) No ____

42. Do you have procedures (equivalent to those used in the facility) assuring the safety and effectiveness of reprocessed dialyzers used by home patients?

a) Yes ____ b) No ____

43. How frequently are reuse procedures practiced by home patients reviewed for compliance?

a) ____ quarterly
b) ____ semi-annually
c) ____ annually
d) ____ other, please specify

FOLLOW-UP REPORT TO THE NETWORK 7
STUDY OF HEMODIALYZER REUSE

Hemodialyzer Reuse Task Force:

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November, 1985

FOLLOW-UP REPORT TO THE NETWORK 7
STUDY OF HEMODIALYZER REUSE
NOVEMBER 1985

BACKGROUND

In June 1985, the Network 7 Medical Directors and Head Nurses received the report of the Hemodialyzer Reuse Task Force, "HEMODIALYZER REUSE IN END-STAGE RENAL DISEASE NETWORK 7: Assessment of current practices, revised Network 7 standards and recommendations for compliance." The report presented results of a questionnaire which assessed reuse procedures practiced in Network 7 facilities. The questionnaire was based on the National Kidney Foundation (NKF) Revised Standards for the Reuse of Hemodialyzers.

The Task Force report recommended standards for hemodialyzer reuse (a modified version of the National Kidney Foundation (NKF) Revised Standards) which were endorsed by the Medical Review Board for use in Network 7. Each dialysis facility which was reusing dialyzers received a list of its procedures that deviated from these standards.

The report of the Hemodialyzer Reuse Task Force listed nine deviations from the National Kidney Foundation's Revised Standards for the Reuse of Hemodialyzers. For two of these deviations, the Task Force recommended modification of the NKF Revised Standards to conform to existing practices in this Network. One modification specified that validation studies of dialyzer performance are necessary only if changes in patient's chemistries or fluid status indicate such a need, providing that properly installed and maintained reuse systems are employed and operated according to the manufacturer's instructions, and providing that patient fluid status and chemistries are carefully monitored (at least monthly) and documented to be stable and satisfactory. The second modification was that patients who are hepatitis B surface antigen positive may participate in hemodialyzer reuse under certain conditions (see page 10-11 of the May 1985 Hemodialyzer Reuse Task Force report). The Task Force report recommended compliance with the seven remaining deviations.

In August 1985, the Network 7 Medical Review Coordinator conducted follow-up to the study of hemodialyzer reuse. A telephone survey of the 14 facilities which were reusing dialyzers was conducted to assess whether steps had been taken to improve compliance with the recommended standards. Nine head nurses, four technicians, and one medical director provided the responses for the 14 facilities. The results of this survey are included in this follow-up report.

RESULTS OF FOLLOW-UP SURVEY

Deviation: Failure to label each used dialyzer with the patient's name and other unique identifying information.

Units involved: 1

Results of follow-up: This unit labels each dialyzer with the patient's name only. Consideration is being given to adding a second identifier, but a decision has not been reached.

Deviation: Failure to maintain a log of febrile reactions.

Units involved: 4

Results of follow-up: All 4 units now maintain logs of febrile reactions.

Deviation: Failure to maintain written protocols, including blood and dialysate cultures during febrile reactions.

Units involved: 6

Results of follow-up: Five units responded that they now have written protocols for blood and dialysate cultures during febrile reactions. One unit is in the process of writing the protocol for these cultures.

Deviation: Failure to treat water with a reverse osmosis membrane, ultrafiltration membrane or 0.45 micron filter.

Units involved: 2

Results of follow-up: One unit has added a reverse osmosis membrane, and the other unit will be installing a new water treatment system in September 1985 which will include a reverse osmosis membrane.

One facility which had been using a 0.45 micron filter is investigating the possibility of adding an ultrafiltration membrane as encouraged in the Task Force recommendations.

Deviation: Failure to document a level of bacterial endotoxin of less than 1 nanogram per milliliter monthly (LAL testing).

Units involved: 10

Results of follow-up: Two of the ten facilities have taken steps to implement LAL testing. Six would like to evaluate LAL testing but need more information about how to perform this test and the associated costs. The remaining 2 units indicated that they do not plan to implement LAL testing.

Deviation: Failure to use 4% formaldehyde in both the blood and dialysate compartments.

Units involved: 4

Results of follow-up: Two of the four units switched from formaldehyde to peracetic acid. One unit increased the concentration of formaldehyde to 4%, and this unit is investigating methods of documenting the concentration of formaldehyde in both compartments. The remaining unit switched to an automated system which does deliver 4% concentration of formaldehyde.

Deviation: Failure to monitor potentially toxic fumes to OSHA standards.

Units involved: 3

Results of follow-up: Two of the three units which did not monitor fumes used peracetic acid for which there is no OSHA standard available. The other unit has switched from formaldehyde to peracetic acid.

Deviation: Failure to obtain informed consent for hemodialyzer reuse.

Units involved: 1

Results of follow-up: This unit is in the process of developing a consent form.

Since January 1985, an additional three units have begun reuse of hemodialyzers and have completed the study questionnaire documenting their policies and procedures. The results from these 3 facilities were combined with the results of the follow-up of the facilities which had been reusing to provide the following updated status report.

STATUS REPORT

As of November, 1985, 17 of 31 Network 7 dialysis facilities were reusing hemodialyzers. Thirteen use a Renatron^{TM} and 4 use the device manufactured by Seratronics.^{TM}

REUSE METHODS AND REUSE DISINFECTANTS

Five units disinfect with a 4% concentration of formaldehyde in both the blood and dialysate compartments. The remaining 12 units use the Renalin^{TM} formulation of peracetic acid as the disinfectant.

SAFETY OF TECHNICAL STAFF

As recommended by the NKF Standards, all units provide:

a. suitable, discreet space for reprocessing and storing used dialyzers;
b. written protocols and training for safe handling of toxic substances;
c. procedures for spills and splashes of toxic substances; and
d. devices for protection from toxic substances.

Twelve of the 17 facilities which reuse report that they control and monitor toxic fumes to or below OSHA standards. Peracetic acid is used for disinfection by the 5 facilities which do not monitor fumes.

DIALYZER INDIVIDUALIZATION

All units are in compliance with the NKF Standards for dialyzer individualization with the following two exceptions:

1. One unit labels reused dialyzers with the patient's name only and does not add other unique identifying information.
2. One unit does not record the number of uses in a record maintained for each dialyzer and in the patient's dialysis record.

DIALYZER SAFETY

Sixteen of seventeen facilities use a reverse osmosis membrane, ultrafiltration membrane or a submicron filter for the water used to formulate cleaning solutions and to rinse dialyzers as prescribed in the NKF Standards. The single noncompliant facility plans to include a reverse osmosis membrane in its new water treatment system.

All 17 units report doing bacterial counts at least monthly in compliance with the NKF Standard with 14 specifying an upper permissible limit of less than 200 colonies per milliliter.

The NKF Standard requires that reuse water contain a level of bacterial endotoxin of less than 1 nanogram per milliliter which is documented by Limulus amoebocyte lysate (LAL) testing not less than monthly. As of August 1985, six facilities were in compliance with this standard. Two facilities were in the process of implementing LAL testing and six facilities expressed a need for more information about how to perform this test. The remaining 3 units do not perform LAL testing and do not have plans to use this procedure.

All 17 units which reuse report that they maintain a log of febrile reactions and have written protocols which include blood and dialysate cultures during febrile reactions.

CONSENT

Sixteen of 17 facilities obtain patient informed consent for the reuse procedure. One unit is in the process of developing a consent form.